

## SUMMARY OF CHANGES

### Phase II Trial of Combined Modality Therapy plus Cetuximab in HIV-Associated Anal Carcinoma

#### Version 10.0

NCI Protocol #: AMC-045

Local Protocol #: AMC-045

NCI Version Date: 04/30/2014

Update Date: 04/30/2014

#	Section	Change Description
1.	<a href="#">Cover Page</a>  <a href="#">Protocol Signature Page</a>  <a href="#">Footer</a>	<i>Changed from:</i> AMC # 045 (Version 9.0) 01/20/2011 NCI Version Date 01/20/2011  <i>Changed to:</i> AMC # 045 (Version 10.0) 04/30/2014 NCI Version Date 04/30/2014
2.	<a href="#">Cover Page</a>  <a href="#">Protocol Roster</a>	<i>Changed from:</i> Lashmi Radjev, MD  <i>Changed to:</i> Lakshmi Radjev, MD
3.	<a href="#">Global</a>	All references to “Adverse Event Expedited Reporting System (AdEERS)” and “AdEERS” were updated to “CTEP Adverse Event Reporting System (CTEP-AERS)” and “CTEP-AERS.”
4.	<a href="#">5.4.1</a>	<i>Changed from:</i> <a href="http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_ctepaers">http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_ctepaers</a>  <i>Changed to:</i> <a href="http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf">http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf</a>
5.	<a href="#">7.1.1</a>	<i>Reference to section number was corrected:</i> Section 7.1.3 to Section 7.2.3
6.	<a href="#">7.2.4.1</a>	<i>Reference to section number was corrected:</i> Section 5.2.2.1 to Section 7.2.4.2
7.	<a href="#">8.3.1</a>	<i>Reference to section number was corrected:</i> Section 8.3.2 to Section 8.4
8.	<a href="#">9.1</a>	<i>Reference to section number was corrected:</i> Appendix XIII to Appendix IV
9.	<a href="#">10.4</a>	<i>Reference to section number was corrected:</i> Section 8.3.2 to Section 8.4

#	Section	Change Description
10.	<a href="#">8.3</a>	<p><u>Changed from:</u> In the rare occurrence when internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at <a href="http://ctep.cancer.gov">http://ctep.cancer.gov</a>) and faxed to 301-230-0159. Once Internet connectivity is restored, an AE report submitted on a paper template must be entered electronically into CTEP-AERS by the original submitter at the site.</p> <p><u>Changed to:</u> A 24-hour notification is to be made to the AMC ODMC by telephone at 301-251-1161, only when Internet connectivity is disrupted. Once Internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.</p>
11.	<a href="#">8.5</a>	<p><u>Changed from:</u> <b>Reporting Secondary AML/MDS/ALL</b> All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the AMC and other appropriate regulatory agencies according to the instructions in section 8.0. Submit the following information within 30 days of an AML/MDS/ALL diagnosis occurring after treatment for cancer on NCI-sponsored trials:</p> <ul style="list-style-type: none"> <li>• A completed NCI/CTEP Secondary AML/MDS/ALL Report Form</li> <li>• A copy of the pathology report confirming the AML/MDS/ALL; and</li> <li>• A copy of the cytogenetics report (if available).</li> </ul> <p><b>AMC Operations Center</b> <b>Fax: (240) 238-2842</b> <b>Phone: (301) 251-1161</b> <b>E-mail: <a href="mailto:amcpm@emmes.com">amcpm@emmes.com</a></b></p> <p><u>Changed to:</u> <b>Reporting Secondary Malignancies</b> A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.</p> <p>CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:</p> <ul style="list-style-type: none"> <li>• Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])</li> <li>• Myelodysplastic syndrome (MDS)</li> <li>• Treatment-related secondary malignancy</li> </ul> <p>Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.</p>
12.	<a href="#">8.6</a>	<p><u>Changed from:</u> All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the AMC and. Submit the following information within 30 days of an AML/MDS/ALL diagnosis occurring after treatment for cancer on NCI-sponsored trials:</p> <ul style="list-style-type: none"> <li>• A completed NCI/CTEP Secondary AML/MDS/ALL Report Form (do not use CTEP-</li> </ul>

#	Section	Change Description
		<p>AERS);</p> <ul style="list-style-type: none"> <li>• A copy of the pathology report confirming the AML/MDS/ALL; and</li> <li>• A copy of the cytogenetics report (if available).</li> </ul> <p>ECOG will forward copies to the NCI.</p> <p><b>ECOG Coordinating Center Mailing Address</b>  ECOG Coordinating Center  FSTRF  ATTN: Adverse Event  900 Commonwealth Avenue  Boston, MA 02215  ECOG Fax Number: (617) 632-2990</p> <p><u>Changed to:</u>  All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the AMC and ECOG in accordance with Section 8.5.</p>
13.	<a href="#">Appendix X</a>	<p><u>Changed from:</u>  APPENDIX X: DATA SAFETY AND MONITORING PLAN  (Version 3.0 • September 4, 2008)</p> <p><u>Changed to:</u>  APPENDIX X: DATA SAFETY AND MONITORING PLAN  (Version 5.0 • January 28, 2014)</p> <p><i>Appendix replaced. Revisions to Version 4.0 of the DSMP included updates to the AMC's procedures for report distribution, medical monitor review, review of dose escalation studies, description of nonvoting DSMB members, and procedures for assuring compliance with adverse event reporting requirements. Revisions to Version 5.0 of the DSMP are limited to the CTEP-AERS change described in Item #3.</i></p>



**AIDS MALIGNANCY  
CLINICAL TRIALS CONSORTIUM**

**AMC PROTOCOL #045:  
Phase II Trial of Combined Modality Therapy plus Cetuximab  
in HIV-Associated Anal Carcinoma**

**A Trial of the AIDS Malignancy  
Clinical Trials Consortium (AMC)**

<b>Funded by:</b>	The National Cancer Institute Division of Cancer Treatment and Diagnosis
<b>Pharmaceutical support provided by:</b>	Bristol-Myers Squibb Company
<b>Agent:</b>	Cetuximab (Erbitux)
<b>Protocol Chairs:</b>	Joseph Sparano, MD Lisa Kachnic, MD David Aboulafia, MD
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Version 10.0, April 30, 2014  
NCI Version Date: April 30, 2014

AMC PROTOCOL SIGNATURE PAGE

I, \_\_\_\_\_, Principal Investigator at site \_\_\_\_\_, agree to conduct and follow this protocol: **AMC Protocol #045 - Phase II Trial of Combined Modality Therapy Plus Cetuximab in HIV-Associated Anal Carcinoma (Version 10.0 dated 04/30/2014)**, as written according to AMC, NCI and FDA guidelines. I understand that no deviations from the above protocol may be made without written permission from the Protocol Chair (s).

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date (mm/dd/yyyy)

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## PROTOCOL ROSTER

### AMC #045

#### Phase II Trial of Combined Modality Therapy plus Cetuximab in HIV-Associated Anal Carcinoma

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## SITES PARTICIPATING IN AMC-045

This trial is open for patient accrual at all AMC sites and participating ECOG institutions.

## SCHEMA

### AMC Protocol # 045

<b>TITLE:</b>	Phase II Trial of Combined Modality Therapy plus Cetuximab in HIV-Associated Anal Carcinoma
<b>STUDY DESIGN:</b>	A phase II trial of combined modality therapy (CMT) consisting of cisplatin, 5-flourouruacil, and irradiation plus cetuximab.
<b>PRIMARY ENDPOINT:</b>	The primary endpoint is local failure rate at 3 years. This trial is designed to detect whether the addition of cetuximab to standard chemoradiation reduces the local failure rate by at least 50%. Secondary endpoints include objective response rate (complete and partial), progression-free survival, relapse-free survival, colostomy-free survival, overall survival, quality of life, and overall toxicity.
<b>SECONDARY ENDPOINTS:</b>	<ol style="list-style-type: none"><li>1. Characterize the effect of CMT plus cetuximab on the underlying HIV condition by describing changes in viral load, CD4 counts, incidence of opportunistic illnesses including the development of AIDS during and in the first year after CMT.</li><li>2. Evaluate the effect of CMT of anal cancer on anogenital HPV infection and anal cytology.</li><li>3. Evaluate EGFR, PI3K, and P-Akt expression in HIV-associated anal carcinoma, and determine whether moderate strong expression is associated with an increased risk of local failure.</li></ol>
<b>POPULATION:</b>	HIV-infected adults with biopsy-proven squamous cell carcinoma of the anus who are candidates to receive CMT with curative intent.
<b>TREATMENT REGIMEN:</b>	<p>All patients will receive CMT with 2 cycles of cisplatin and 5-FU chemotherapy, given concurrently with radiation therapy. CMT consists of:</p> <ul style="list-style-type: none"><li>• Cetuximab 400 mg/m<sup>2</sup> IV Day -7 (1 week before the cycle 1, Day 1 cisplatin/5-FU and RT), then 250 mg/m<sup>2</sup> IV Days 1, 8, 15, 22, 29, 36 and 43 (a minimum of 6 and a maximum of 8 doses of cetuximab will be administered, including the loading dose).</li><li>• Cisplatin 75 mg/m<sup>2</sup> IV on Day 1 (cycle 1) and Day 29 (cycle 2)</li></ul>

- 5-FU 1000 mg/m<sup>2</sup>/day by continuous intravenous infusion on Days 1-4 (cycle 1) and Days 29-32 (cycle 2)

NOTE: All patients will be seen by the radiation oncologist prior to induction chemotherapy. The radiation therapy treatment planning will be based on pre-chemotherapy tumor volumes. Irradiation to tumor site and inguinal nodes beginning on cycle 1, Day 1 cisplatin/5-FU (minimum 45.0 Gy [5 weeks if given on schedule and without interruption], maximum 54.0 Gy [6 weeks if given on schedule and without interruption]). IMRT may be used at the discretion of the treating physician.

Treatment modifications:

- The second cycle of chemotherapy may be reduced and/or delayed due to hematologic toxicity or other toxicities (see [sections 7.1](#), [7.2.1](#), and [7.2.2](#))
- Irradiation held for excessive bone marrow, gastrointestinal, or cutaneous toxicity (see [section 7.2.3](#))
- Cetuximab held if irradiation held (or chemotherapy plus irradiation held) because of toxicity (see [sections 7.1.1](#) and [7.2.4](#))

**DURATION:**

Patients will be followed on study for up to 5 years.

**SAMPLE SIZE:**

45 eligible and evaluable patients (50 total assuming 10% ineligibility).

**EXPECTED ACCRUAL RATE:**

Two eligible/evaluable patients per month. The trial is expected to take approximately 24 months to complete.

## 1.0 INTRODUCTION

### 1.1 Epidemiology

The incidence of anal cancer in the general population is nearly a log lower than the current rate of cervical cancer at only 0.9 cases/100,000. It is expected that there were approximately 4,000 cases diagnosed in 2004, with nearly 600 deaths.<sup>[1]</sup> This represents a doubling in incidence in recent decades, and is likely due to changing sexual behavior within the general population.<sup>[2]</sup> Correlates of homosexual behavior in men (for instance never having been married) were shown to correlate with an increased risk of anal cancer nearly two decades ago.<sup>[3, 4]</sup> A number of studies have since confirmed the relationship between anal cancer and receptive anal intercourse in men. Even before HIV became widely epidemic, the incidence in men with a history of receptive anal intercourse exceeded the incidence of cervical cancer prior to the introduction of Pap smear screening at 35 per 100,000.<sup>[5]</sup> Merged cancer and AIDS registry data indicate that anal cancer is 80-fold more frequent than expected in individuals with a diagnosis of AIDS.<sup>[6, 7]</sup> Other support includes data from the U.S. AIDS-Cancer registry match.<sup>[8]</sup> This study linked AIDS and cancer registries for both HIV-positive men and women from 11 state or metropolitan locations between 1995 and 1998 to study cancer incidence in more than 309,000 HIV-infected individuals. The overall risks of HPV-associated cancers and their in situ precursor lesions were elevated for all anogenital sites studied. The relative risks for cervical cancer, vulva or vaginal cancer, and penile cancer were elevated at 5.4, 5.8 and 3.7 respectively. The relative risk of 6.8 (of 134 individuals) for anal cancer in women included a tremendously increased risk for young HIV-positive women under the age of 30. At this age, the risk is normally extremely low in the absence of HIV infection. The relative risk for HIV-positive men was 37.9, again with the greatest increased risk seen in the youngest group. As expected, the HIV exposure category of homosexual contact had the strongest association with anal cancer, but it was notable that all HIV exposure categories, including intravenous (IV) drug use, transfusion and for women, heterosexual contact, were associated with increased risks of anal cancer.

HPV infections of the anogenital tract are sexually transmitted and endemic worldwide.<sup>[9]</sup> HPV is believed to be the primary initiating event for anogenital neoplasia as validated by histological, molecular, and epidemiological evidence. HPV DNA has been identified in more than 99% of cervical squamous cell carcinomas and in most anal cancers. In a case control study by Frisch, HPV DNA was detected in 88% of 388 cases of anal cancer and in none of 20 colon cancer control specimens.<sup>[10]</sup> HPV 16, the most common HPV type found in cervical cancer, was found in 73% of these cases. There are nearly 100 HPV subtypes that differ in tissue tropism (mucosal or cutaneous) and oncogenicity (high and low risk). Most cases of anal and cervical dysplasia or cancer contain high risk HPV such as 16 or less frequently 18, 31, 33, or 45. Oncogenic HPV types have E6 and E7 gene products that have tight binding efficiencies to p53 and pRb, respectively. The reduced levels and function of p53 and pRb within the cell lead to inhibition of apoptosis, cell cycle dysregulation, and genetic instability.

## 1.2 Treatment of Anal Carcinoma in Immunocompetent Patients

Standard therapy consists of chemotherapy and radiation therapy, which results in about 60-70% disease-free survival and local failure rates of about 30-40%.<sup>[11]</sup> Randomized trials have clearly established that combined modality therapy (CMT) consisting of mitomycin-C, 5-fluorouracil (5-FU), and irradiation results in improved local control and disease-free survival compared with irradiation alone (Table 1). In addition, one phase III trial has demonstrated that the addition of mitomycin-C to 5-FU and irradiation further improves local control and disease-free survival.

**Table 1: Phase III Trials of Combined Modality Therapy of Anal Carcinoma in Immunocompetent Patients**

Study/Arms	No.	Local Failure	Disease-free Survival	Overall Survival
UKCCCR[12]				
RT alone	290	59%	61%	58%
RT + 5-FU + mitomycin	295	36% (p<0.0001)	72%	65%
EORTC[13]	110			
RT alone		50%	NR	52%
RT + 5-FU + mitomycin		40% (p=0.02)		59%
Intergroup [14]				
RT + 5-FU	145	NR	51%	ND
RT = 5-FU + mitomycin	146		73% (p=0.0003)	

Abbreviations: NR - not reported; ND – no difference

Several phase II trials have evaluated substituting cisplatin for mitomycin-C. Mitomycin-C has only modest anti-tumor activity when used alone for squamous cell cervical cancer (SCCA), and is associated with long term toxic effects on the kidney, lung, and bone marrow. The platinum compounds are considered more effective than mitomycin in the treatment of other squamous cell carcinomas, and are now commonly used as a component of the first line therapy for cervical cancer, head and neck cancer, and esophageal cancer. Several phase II trials in anal cancer have shown very promising results in anal carcinoma when cisplatin was combined with irradiation, and/or used as component of neoadjuvant therapy prior to irradiation.<sup>[15] [16, 17]</sup> An ongoing phase III RTOG trial (R9811) is comparing mitomycin-C (10 mg/m<sup>2</sup> Days 1 and 29) and 5-FU (1000 mg/m<sup>2</sup> Days 1-4 and 29-32) versus cisplatin (75 mg/m<sup>2</sup> Days 1, 29, 57, 85) and 5-FU (1000 mg/m<sup>2</sup> Days 1-4, 29-32, 57-60, 85-88) in combination with radiation therapy in immunocompetent patients with anal carcinoma given concurrently with radiation therapy. For the mitomycin-C/5-FU arm, irradiation begins on Day 1 of cycle 1. For cisplatin/5-FU arm, irradiation begins concurrently beginning on Day 1 of cycle 3 (or Day 57 of therapy). All patients receive an initial radiation dose of 30.6 Gy in 17 1.8 Gy fractions to a large pelvic field (superior border at L5-S1), followed by a field reduction (reduce superior border to inferior level of S1) for an additional 14.4 Gy in eight 1.8 Gy fractions. For patients with high-risk disease (T3, T4, or N+ lesions and T2 lesions with residual cancer after 45Gy), an additional 10-14 Gy (2 Gy/fraction) is delivered to gross primary or nodal disease plus a 2-2.5 cm margin for a total dose of 55-59 Gy within the boost field. As of January 2004, a total of 502 of the required 650 patients have been

enrolled on the study. Thus far, there appears to be less toxicity associated with the cisplatin/5-FU arm that would be of particular concern in an HIV-positive population, including grade 4 bone marrow toxicity (34% vs. 49%), grade 3-4 infection/febrile neutropenia (14% vs. 27%), and less overall grade 4 toxicity (43% vs. 62%) and grade 5 toxicity (0% vs. < 1%). Preliminary data from this ongoing study and multiple previous phase II studies indicates that cisplatin/5-FU and irradiation is a reasonable treatment option for anal carcinoma.

### 1.3 Anal Carcinoma in Patients with HIV Infection

As previously described in [section 1.1](#), the risk of invasive squamous cell carcinoma of the anus is substantially increased in patients with HIV infection.<sup>[18]</sup> All available data regarding treatment of HIV-infected individuals with anal cancer have been retrospective in nature, and patients were treated in the era prior to the routine use of highly active antiretroviral therapy (HAART). The studies published or presented thus far are outlined in the Table 2. This summary outlines the limitations of the available information, and highlights the need for a prospective clinical trial performed in the HAART era. In most studies, patients received combined modality therapy consisting of mitomycin-C, 5-FU, and variations of standard doses/fractions of irradiation. HIV-positive patients seem to experience more acute toxicity and poorer survival than immunocompetent patients with anal carcinoma. The largest study was a retrospective review (personal communication, T. Allen-Mersch) that included 68 patients treated with combined modality therapy at four different centers in London and New York, including Montefiore Medical Center. The mean age was 44 years, median CD4 count was 255/ $\mu$ L, and 76% were receiving HAART at the time of diagnosis. Most patients received mitomycin-C, 5-FU, and irradiation. At the time of the analysis, 21 patients (31%) had died, including 14 from disseminated anal carcinoma (21%), and 7 patients (10%) from other causes. Approximately 35% had local failure at one year. The incidence of grade 3-4 gastrointestinal, cutaneous, and hematologic toxicity was approximately, 21%, 41%, and 34%, respectively. The majority of the toxic effects were grade 3 events, with grade 4 gastrointestinal, cutaneous, and hematologic toxicity occurring in only 0%, 7%, and 13%, respectively (although there may have been under-ascertainment of toxicity in this retrospective study). Fifteen patients (22%) required radiation treatment breaks due to toxicity.

**Table 2: Treatment of Anal Carcinoma in HIV-Infected Individuals**

Reference	No.	Conclusion
Hoffman[19]	17	Patients with CD4> 200 have a better outcome
Holland [20]	7	HIV+ patients have more toxicity than HIV- controls
Chadha [21]	9	HIV+ patients have more toxicity than HIV- controls but comparable local control
Peddada [22]	8	Good local control and acceptable toxicity with 5-FU plus reduced dose irradiation (30Gy)
Hocht [23]	4	Mild acute reactions, short followup
Place [24]	23	40% one year mortality, 80% 5 year mortality
Kim [25]	13	HIV+ patients have more acute toxicity (80% vs. 30%)

Reference	No.	Conclusion
		and poorer disease control (62% vs. 85%)
Cleator[26]	12	60% 2 year survival and 50% grade 3-5 acute toxicity
Allen-Mersch	68	66% disease-free survival and 85% overall survival at 1 year

#### 1.4 Rationale for Combining Cetuximab with CMT for Anal Carcinoma

The epidermal growth factor receptor (EGFR), whose ligands include EGF and transforming growth factor (TGF)-alpha, is a member of the ErbB family of receptors that is broadly expressed in epithelial cancers, including squamous cell carcinoma of the anus. Cetuximab is chimeric IgG1 monoclonal antibody that binds EGFR with high specificity and with greater affinity than its ligands, thus blocking ligand-induced activation of EGFR. Cetuximab was recently approved by FDA in combination with irinotecan for patients with EGFR-expressing metastatic colorectal carcinoma who have developed resistance to irinotecan therapy.<sup>[27, 28]</sup> The response rate for cetuximab alone was 11%, compared with 23% for cetuximab plus irinotecan (23%; p=0.007). There was no correlation between response and EGFR expression, either as a percentage of EGFR-positive tumor cells or as the maximal staining intensity per cell. However, there was a significantly higher response rate among patients with developed acneform skin reactions compared with those who did not in both the combination group (26% vs. 6%; p=0.005) and the monotherapy group (13% vs. 0%).

Cetuximab has been shown to prolong survival in patients with locally advanced squamous cell carcinoma of the head and neck<sup>[28]</sup> and enhance the effectiveness of cisplatin in advanced head and neck carcinoma<sup>[29]</sup> (Table 3), and may be safely combined with oxaliplatin and 5-FU in colorectal cancer.<sup>[30]</sup> In the head and neck trial, patients were randomized to receive irradiation alone or in combination with cetuximab (400 mg/m<sup>2</sup> IV week 1, then 250 mg/m<sup>2</sup> weekly in weeks 2-8). Physicians could select the radiation fractionation schedule, which was equally distributed in the two arms, and which were substantially higher than the doses typically used for anal carcinoma (45-54 Gy for anal carcinoma compared with 70-76.8 Gy for the head and neck trial [70 Gy in 35 daily fractions over 7 weeks; 72-76.8 Gy in 60-64 fractions twice daily over 6 – 6<sup>1/2</sup> weeks; or concomitant boost, with 72 Gy given in 42 fractions over 6 weeks]). The addition of cetuximab led to improved local regional control at 1 year (69% vs. 59%; p=0.02) and 2 years (56% vs. 48%; p=0.02), as well as significantly improved survival (57% vs. 44% at 3 years p=0.002). Although there were significantly more skin reactions and infusion reactions associated with cetuximab, there were no significant differences in the incidence of mucositis/stomatitis, xerostomia, dysphagia, or fatigue.

**Table 3. Phase III Trials of Cetuximab in Squamous Cell Carcinoma of the Head and Neck**

Study/ Patient Population	Arms	No.	Efficacy	Comment
Bonner et al (ASCO, 2004) Locally advanced disease at Initial	RT alone RT + cetuximab	212 211	Median survival 28 mo. 58 mo. (p=0.02)	More grade 3-4 skin reaction with cetuximab (34% vs. 18%; p=0.0003)



Study/ Patient Population	Arms	No.	Efficacy	Comment
presentation				but no difference in grade 3-4 mucositis (55% vs. 52%)
Burtress (ASCO 2002) Metastatic disease or locally Recurrent after prior RT	Cisplatin + placebo Cisplatin + cetuximab	60 63	Response rate 9% 23% (=0.0508)	Trend toward improved 2 year survival (29% vs. 17%) for cetuximab

## 1.5 Rationale for the Proposed Trial Design

We propose a phase II trial of cetuximab plus cisplatin, 5-FU, and irradiation in patients with anal carcinoma and HIV infection. Given the potential for less bone marrow suppression and more favorable safety profile reported for cisplatin/5-FU/RT, this will be the treatment regimen employed in our trial rather than mitomycin-C and 5-FU. Given the high prevalence and degree of EGFR expression by squamous cell carcinoma of the anus and the promising data for combining cetuximab with either cisplatin or irradiation in squamous cell carcinoma of the head and neck, there is clear rationale for evaluating this strategy in anal carcinoma. The results of this phase II trial may form the basis for an experimental arm of a future phase III trial evaluating cisplatin/5-FU/RT +/- cetuximab, or perhaps cetuximab/RT +/- cisplatin/5-FU. This trial is designed to detect whether the addition of cetuximab to standard chemoradiation reduces the local failure rate by at least 50% at 3 years.

In this proposed trial, we will give cisplatin and 5-FU for only two cycles concurrently with irradiation and cetuximab; this differs slightly from the R9811 trial, in which two cycles of induction cisplatin/5-FU are given alone, followed by two cycles of cisplatin/5-FU followed given concurrently with irradiation. The reasons for using only two cycles of chemotherapy is justified in patients with HIV infection and anal carcinoma on the following grounds: (1) the duration of treatment will be reduced by 50%, which should result in less chemotherapy-related toxicity, a particular concern in patients with HIV infection; (2) the concurrent administration of cetuximab, chemotherapy, and radiation therapy offers greater potential for cetuximab to enhance the effects of both chemotherapy and irradiation; and (3) there is no evidence for a benefit from a course of induction chemotherapy prior to combined chemoradiotherapy in squamous cell carcinoma arising in other sites. For example, in head and neck carcinoma, induction chemotherapy has had little impact on reducing locoregional and distant failures despite rapid reduction of tumor size in most patients treated with induction chemotherapy.<sup>[31]</sup> Should the results of this trial indicate that this combination to be feasible, tolerable, and effective, we will consider amendment of this study to evaluate administration of two cycles of cisplatin/5-FU given before combined modality therapy, as given in trial R9811

Anal carcinoma and its treatment may produce significant morbidity that is not adequately captured by adverse event (AE) grading systems, including issues such as continence and sexual function. This study will therefore include quality of life instruments that are specifically designed for individuals with anal carcinoma, and will provide useful information regarding these important issues.

IMRT (Intensity Modulated Radiation Therapy) has become the standard way to deliver radiation therapy in the treatment of head-and-neck <sup>[40-43]</sup> and prostate cancers <sup>[44]</sup>. In anal cancer, IMRT has the potential to reduce prescription dose to normal structures such as small and large bowel, bladder, external genitalia, femoral head, bone marrow and skin, thereby reducing toxicity. However, very little has been published using IMRT for the treatment of this disease. This is mainly due to complexities associated with accurate target delineation of both primary and sub-clinical disease in the pelvis region.

There have been two published studies looking into the advantages of IMRT in treating anal cancer. Milano, et al. <sup>[45]</sup> reported that the dose to normal structures is reduced when using IMRT as compared to 3-D AP-PA planning. IMRT yielded excellent local control (82% at 2 years) and was well tolerated with most patients experiencing only mild or moderate side effects and few patients experiencing treatment breaks (13 of 17 had no treatment breaks). A dosimetric study by Chen, et al. <sup>[46]</sup>, demonstrated that conformal avoidance IMRT technique achieves comparable planning target volume (PTV) coverage compared with other approaches while at the same time significantly sparing the surrounding Organs at Risk.

Boston Medical Center and Massachusetts General Hospital have recently developed a method of delivering a single-phase IMRT plan using a dose-painting (DP-IMRT) technique. Six patients with squamous cell carcinoma (stage T2N0 and above) of the anal canal were treated with DP-IMRT and concurrent chemotherapy<sup>[47]</sup>. The DP-IMRT dose prescriptions were 50.4 Gy at 1.8 Gy/fraction to the primary tumor and 42 Gy at 1.5 Gy/fx to the elective nodes for T2 N0 disease, or 54 Gy at 1.8 Gy/fx to the tumor and 45 Gy at 1.5 Gy/fx to the elective nodes for T3-4/N+ disease. Involved nodes were prescribed 54 Gy at 1.8 Gy/fx if > 3 cm in size or 50.4 Gy at 1.68 Gy/fx if ≤ 3 cm. For the dosimetric analysis, the DP-IMRT plans were compared with optimal, 3-D CT-based conformal therapy (CRT) per RTOG 98-11 design and doses. For the early clinical analysis, acute toxicity was assessed using the RTOG scoring system. The mean percentage of the primary clinical target volume receiving the prescription dose was 97% for both the DP-IMRT and CRT plans. DP-IMRT provided better tissue sparing of most normal structures. The acute toxicity experienced by the six patients treated with DP-IMRT was generally well-tolerated. All patients completed therapy as prescribed, and no patient required a treatment break of over one week. Four patients experienced grade ≥ 2 skin toxicity; three had grade ≥ 3 hematologic toxicity, and no patients had grade ≥ 3 GI toxicity. No patient experienced inguinal skin desquamation; however since perianal tissue is target, moist desquamation in the anus was observed. All patients achieved a complete tumor response based on clinical and radiographic assessment.

Because of the potential advantages of IMRT, this protocol allows use of both standard and conformal planning techniques. The efficacy endpoint will be evaluated using all patients treated, included conventional RT and IMRT. Toxicity will be evaluated in the entire group, and separately in the IMRT group and conventional RT group. An exploratory analysis of the primary endpoint (local failure) will be conducted based on the type of radiation received (RT and IMRT); local failure will be monitored

continuously for both treatment strata (conventional RT vs. IMRT) throughout the course of the study. The trial may be amended to exclude IMRT if it becomes apparent that IMRT results in inferior disease control or worse toxicity. For conformal techniques, approved benchmarks must be on file at QARC. Centers participating in this protocol using 3D conformal techniques are required to complete the 3D Benchmark; those treating with IMRT must complete the IMRT Questionnaire and either the QARC Benchmark or irradiate the RPC's IMRT head and neck phantom. The Benchmark material can be obtained from the Quality Assurance Review Center ([www.QARC.org](http://www.QARC.org)). Contact the RPC (<http://rpc.mdanderson.org/rpc>) for information regarding their IMRT phantoms.

## 1.6 Laboratory Correlates

Few studies have evaluated the effect of biological features of anal carcinoma and disease control. Bonin, et al. evaluated p53 expression in tumor specimens from patients enrolled on an RTOG trial evaluating 5-FU/radiation +/- mitomycin; 48% of the 64 specimens evaluated over-expressed p53 by immunohistochemistry, with a trend for inferior local control, disease-free survival, and overall survival for those patients having tumors that demonstrated p53 overexpression.[32] However, squamous cell carcinoma of the anus shares several biological characteristics with head and neck carcinoma that may be relevant to this proposal, including a high prevalence of EGFR expression (nearly all in both cases) and HPV infection (most anal carcinoma [33] compared with about 35% for head and neck carcinoma.[34, 35]) Several studies have evaluated the role of signal transduction pathways and prognosis in head and neck cancer, and in particular their relation to treatment resistance and local control. For example, Gupta, et al. reported that expression of phosphorylated Akt (P-Akt), a downstream target of PI3K, was associated with inferior local control in patients with squamous cell carcinoma of the head and neck treated with irradiation (2 year local control rate 71% for 2-3+ P-Akt staining by IHC, compared with 100% local control rate for 0-1% staining).[36] Of the 38 head and neck cancers evaluated, 79% demonstrated strong (3+) EGFR expression, and 66% demonstrated moderate to strong (2+ - 3+) expression of P-Akt. In addition, Gupta, et al. reported that pharmacological inhibition of EGRF, Ras, and PI3K led to radiosensitization of SQ20B squamous cell carcinoma in vitro.

In this trial, we plan to evaluate EGFR, PI3K, and P-Akt expression in paraffin-embedded tumor specimens, and to perform anal swabs for HPV detection and genotyping, with all studies to be performed in the Palefsky laboratory. We hypothesize that similar to the findings reported by Gupta in a relatively small number of patents with head and neck carcinoma (N=38), moderate to strong P-AKT expression will be associated with an increased risk of local failure. Polymerase chain reaction (PCR) for anal HPV testing will be performed as published previously and will detect 39 different HPV types.[37] The swab material provides a sampling of the entire anal canal but this may or may not directly reflect the HPV type in the tumor. For this reason, we will also perform HPV testing from the anal biopsy specimens using methods published previously.[38] EGFR, PI3K, and P-Akt expression will be studied using quantitative real-time PCR (Q-RT-PCR). RNA will be extracted from the samples in the Palefsky laboratory. Quantitative PCR will be done on anal tissues using techniques performed by

Dr. Palefsky's group and the UCSF Comprehensive Cancer Center Genome Analysis Core. We will use two-step Q-RT-PCR. For evaluation by Q-RT-PCR, RNA will be extracted from the formalin-fixed paraffin-embedded (FFPE) anal epithelium tissues. RNA obtained from each sample will be reverse transcribed and amplified in triplicate for assessment of the above genes as well as three housekeeping genes. The resulting cDNA will be amplified in a two-step real-time PCR to quantify gene expression of our target genes. Each sample will be evaluated in triplicate. The outcome of interest will be the mean Ct value (the cycle number at which the increase in fluorescence, and therefore cDNA, is logarithmic) for each anal sample that will be analyzed by either the standard curve method or the comparative Ct method. The comparative Ct method is preferred and will be used if possible. The results of these studies with anal cancer samples will be compared with those of normal tissues and different grades of anal intraepithelial neoplasia (AIN) obtained either from Dr. Palefsky's Anal Neoplasia Clinic or from the AIDS Clinical Specimen Resource (ACSR). We will study three samples each of normal, AIN 1, AIN 2 and AIN 3 tissues for comparison with the anal cancer samples. In addition to Q-RT-PCR, we will examine levels of EGFR, PI3K and P-Akt expression using immunohistochemistry (IHC) in the FFPE tissues using the method of Gupta, et al. In these studies, strength of IHC staining will be graded and the results correlated with treatment outcome. We will also compare the IHC results to the Q-RT-PCR results. In addition to the above, the EGFR gene from anal cancer specimens will be sequenced to determine if mutations are present. Finally, cDNA will be stored should we wish to study expression of other genes in the future. Relative expression levels or DNA copy number measurements of genes are performed using the 5' fluorogenic nuclease assay in Q-RT-PCR. The basis for this system is to continuously measure PCR product accumulation using a dual-labeled fluorogenic oligonucleotide probe, called a TaqMan™ probe. This probe is composed of a short (ca. 20-25 bases) oligonucleotide that is labeled with two different fluorescent dyes. On the 5' terminus is a reporter dye and on the 3' terminus is a quenching dye. The oligonucleotide sequence is homologous to a target sequence in the genome and PCR primers encompassing the probe sequence are added. Briefly, the protocol involves: (1) Tissue isolation, RNA purification and reverse transcription – Tissue samples are obtained from FFPE anal biopsy specimen. For total RNA isolation from FFPE tissues, three 10 µm thick sections will be cut from each tissue block. The High Pure RNA Paraffin Kit (Roche) will be used as reported by Bibikova, et al.[39] Samples are first deparaffinized and RNA isolation then performed. Proteinase K digestion time will be 12 hours for each sample. All purification, DNase treatment, and other steps were performed according to the manufacturer's protocol. After total RNA isolation, samples will be stored at -80°C until use. Deparaffinization is performed using 800 µl Hemo-De (or Xylol) and ethanol. Total RNA from entire sections of tissue is assessed with a Bioanalyser to determine RNA quality. Purified RNA (1/3 of total obtained) is reverse transcribed in 20 µl volume following the manufacturer's instructions to yield cDNA (80 U RNase H- Superscript II), 250 ng random hexamers (Invitrogen), 20 nmoles dNTPs each, 20 U RNase inhibitor (Superase In, Ambion). Following reverse transcription, an amplification step is performed. (2) cDNA Amplification – Individual RT-PCR reactions are set up using individual sets of "inner" primers for each gene of interest. This includes separate reactions for the housekeeping genes. Amplification occurs on a 7700 or 7900 Sequence Detection System (Applied Biosystems): 1 cycle at

50°C for 2 minutes, 1 cycle at 95°C for 10 minutes, 40 cycles at 95°C for 15 seconds, 60°C for 1 minute. Great care is given to the analysis of all raw Ct values obtained from these amplifications. Amplifications resulting in Ct values <6 (threshold 0.04) are repeated with smaller amounts of input pre-amplification cDNA to ensure that amplification plateaus are not reached. Outer and inner primers were designed with the “Primer Express” software (Applied Biosystems). Amplicon lengths for outer primers are kept <250 bp. The analysis will be primarily exploratory because of the limited sample size. From the Q-RT-PCR data, an average Ct value is calculated from triplicate reactions and analyzed by the standard curve approach. Averaged Ct values are then normalized (to adjust for different amounts of cDNA in each reaction) using the raw values obtained for each separate collection of the housekeeping control gene from the same patient. Relative expression levels of the same gene between two samples are determined according to  $\Delta$  Ct values. A  $\Delta$ Ct value < 1 is considered no change. Statistical evaluation is conducted using the rank test. After Ct values are normalized using the raw housekeeping control gene values, log Ct values are obtained for all three genes because of the logarithmic correlation between Ct value and gene expression levels. Another quantitative approach to evaluate relative gene expression is termed the comparative Ct method. This involves comparing the average Ct values of the samples of interest with the average of a control or calibrator such as RNA from normal tissue. The Ct values of both the calibrator and the samples of interest are normalized to an appropriate endogenous housekeeping gene. The comparative Ct method is also known as the  $2^{-\Delta\Delta Ct}$  method, where  $\Delta\Delta Ct = \Delta Ct_{\text{sample}} - \Delta Ct_{\text{reference}}$ . Here,  $\Delta Ct_{\text{sample}}$  is the Ct value for any test sample normalized to the endogenous housekeeping gene and  $\Delta Ct_{\text{reference}}$  is the Ct value for the calibrator (e.g., normal tissue sample) also normalized to the endogenous housekeeping gene. For the  $\Delta\Delta Ct$  calculation to be valid, the amplification efficiencies of each target gene and the endogenous reference must be approximately equal. This must be established by a validation experiment looking at how  $\Delta Ct$  varies with template dilution. If the plot of cDNA dilution versus delta Ct is close to zero, it implies that the efficiencies of the target and housekeeping genes are very similar. If a housekeeping gene cannot be found whose amplification efficiency is similar to the target genes, then the standard curve method is preferred. The comparative Ct method will be used if possible as the need for a standard curve is eliminated. This increases throughput because wells no longer need to be used for the standard curve samples. It also eliminates the adverse effect of any dilution errors made in creating the standard curve samples as the target and endogenous control amplifications are run in separate tubes.

## **2.0 OBJECTIVES**

### **2.1 Primary Objective**

The primary endpoint is local failure rate at 3 years.

### **2.2 Secondary Objective**

Secondary endpoints include objective response rate (complete and partial), progression-free survival, relapse-free survival, colostomy-free survival, overall survival, quality of life, and overall toxicity.

### **2.3 Correlative Science Objectives**

1. Characterize the effect of CMT on the underlying HIV condition by describing changes in viral load, CD4 counts, and incidence of opportunistic illnesses including the development of AIDS during and in the first year after CMT
2. Evaluate the effect of CMT of anal cancer on anogenital HPV infection and anal cytology.
3. Evaluate EGFR, PI3K, and P-Akt expression in HIV-associated anal carcinoma, and determine whether moderate strong expression is associated with an increased risk of local failure.

### **3.0 PATIENT SELECTION**

#### **3.1 Inclusion Criteria**

1. Histologically proven stage I-IIIB (see [Appendix II](#)) invasive anal canal or perianal (anal margin) squamous cell carcinoma. This may include tumors of non-keratinizing histology such as basoloid, transitional cell, or cloacogenic histology. Patients with well differentiated Stage I anal margin cancer are not eligible.
2. Documented HIV infection. Documentation may be by antibody detection, culture, or quantitative assay of plasma HIV RNA.
3. No prior chemotherapy and no prior irradiation for this malignancy. Patients with a history of prior irradiation to the planned irradiation field for another condition (e.g., Kaposi's sarcoma) may be eligible after consultation with the radiation oncology study co-chair.
4. Adult patients, 18 years of age or older.
5. Karnofsky Performance Status > 60 %.
6. Adequate hematologic function within 14 days of study enrollment: Hemoglobin > 10 g/dL; Platelet count > 100,000/mm<sup>3</sup>; ANC > 1500/mm<sup>3</sup>. Patients receiving transfusion, erythropoietin, or myeloid growth factor support will be eligible for this study as long as these requirements have been stable for a minimum of 2 weeks prior to enrollment.
7. Creatinine < 1.5 X the upper limits of normal (ULN) or a creatinine clearance above 60 mL/min within 14 days of study enrollment.
8. Adequate hepatic function within 14 days of study enrollment: AST and ALT < 3 X ULN, total bilirubin < 2 X ULN unless related to antiretroviral use, then the direct bilirubin must be < 2 X ULN.
9. Able and willing to provide written consent.

#### **3.2 Exclusion Criteria**

1. Acute active, serious, uncontrolled opportunistic infection. Patients with a CD4 count < 50/μL will be excluded if they have had an opportunistic infection within the past 6 months, or if there is evidence of resistance to antiretroviral therapy (i.e., HIV viral load > 400 copies/mL despite antiretroviral therapy).
2. Prior invasive malignancy diagnosed within the past 24 months, excluding in situ cervical cancer, anal dysplasia or carcinoma in situ, non-melanoma skin carcinoma, Kaposi's sarcoma that has not required systemic chemotherapy within the past 24 months.
3. Grade 2, 3, or 4 neuropathy.
4. Severe (grade 3 or 4) or poorly controlled diarrhea.
5. Pregnancy or breast-feeding. Radiation therapy to the pelvis is contraindicated during any stage of pregnancy. Both chemotherapy drugs (5-FU and cisplatin) are contraindicated during pregnancy and breast-feeding. The 5-FU package insert states "compounds that inhibit DNA, RNA and protein synthesis might be expected to have

adverse effects on post-natal as well as pre-natal development. The effects of cetuximab on a developing fetus are unknown, and may cause harm.”

6. A medical or psychiatric illness that precludes ability to give informed consent or is likely to interfere with the ability to comply with the protocol stipulations.

### **3.3 Enrollment Procedures**

#### **3.3.1 AMC Investigators**

This study will be available for enrollment at all AIDS Malignancy Clinical Trials Consortium (AMC) sites. Sites must have this protocol approved by their Institutional Review Boards (IRBs) and be registered with the AMC Operations Center before they may enroll patients. The site must identify at the time of registration whether the patient is being treated with standard RT or IMRT.

After it has been determined that the patient is eligible and an informed consent has been signed by the patient, the patient must be registered on-line via the AMC AdvantageEDC<sup>SM</sup> internet data entry system. Registration will be accepted from the AMC main or affiliated institutions.

The participating site will ensure the patient meets all eligibility criteria prior to completing the protocol-specific eligibility checklist. Patients will be enrolled on-line via the AMC AdvantageEDC<sup>SM</sup> internet data entry system no more than one week prior to the initiation of treatment (enrollment one day prior to or on the day of treatment is strongly encouraged). Once the eligibility checklist is submitted and eligibility is confirmed, a system generated confirmation email will be sent to the enroller with a subject-specific ID that will be used to access the case report forms (CRFs). If the on-line system is inaccessible, the site should notify the AMC Operations Center (via email at [amcpm@emmes.com](mailto:amcpm@emmes.com) or phone at 301-251-1161) for further instructions.

#### **3.3.2 Registration – ECOG Investigators**

##### **➤ Submitting Regulatory Documents**

Before an ECOG Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office  
Coalition of National Cancer Cooperative Groups  
1818 Market Street, Suite 1100  
Philadelphia, PA 19102  
Fax: 215-569-0206

##### **➤ Required Protocol Specific Regulatory Documents**

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.



*Note: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.*

3. A. CTSU IRB Certification Form.

**OR**

B. HHS 310 Form.

**OR**

C. IRB Approval Letter

*Note: The above submissions must include the following details:*

- *Indicate all sites approved for the protocol under an assurance number.*
- *OHRP assurance number of reviewing IRB.*
- *Full protocol title and number.*
- *Version Date*
- *Type of review (full board vs. expedited).*
- *Date of review.*
- *Signature of IRB official.*

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed **[http://www.ctsu.org/rss2\\_page.asp](http://www.ctsu.org/rss2_page.asp)**.

If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail **[CTSUContact@westat.com](mailto:CTSUContact@westat.com)**. Monday through Friday, 9:00 a.m. to 6:00 p.m.

Patients must not start protocol treatment prior to registration.

Treatment should start within five working days after registration (enrollment one day prior to or on the day of treatment is strongly encouraged).

Institutions may begin to register eligible patients to this study by completing the AMC-045 Eligibility Worksheet. A copy of this worksheet can be downloaded from the ECOG web site located under "Protocol - Complete Protocol Information" for AMC045. After completing these questions you must also complete the ECOG registration worksheet via the ECOG webpage using the Web-based Patient Registration Program (**<https://webreg.ecog.org>**). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022. Please note that a password is

required to use this program. The following information will be requested: Protocol Number; Investigator Identification (including institution and/or affiliate name and investigator's name); Eligibility Verification and patient demographics. Patients must meet all of the eligibility requirements listed in [Section 3.0](#). After completing the ECOG registration worksheet on the web, the institution must call the Central Randomization Desk at the ECOG Coordinating Center to provide the Transaction ID # at (617) 632-2022, Monday-Friday, between the hours of 9:00 a.m. and 4:30 p.m. ET. ECOG members should not call the AMC directly. Immediately after phoning the ECOG Randomization Desk, the institution must fax the NCIC CTG Eligibility Worksheet to the NCIC CTG Central office at (613) 533-2941.

The ECOG Randomization Desk will complete the randomization process and call the institution back to relay the treatment assignment for the patient. The ECOG Coordinating Center will forward a confirmation of treatment assignment to the ECOG participating institution.

## **4.0 REQUIRED DATA**

### **4.1 Records to be Kept**

CRFs will be provided for each subject via the AMC AdvantageEDC<sup>SM</sup> internet data entry system upon enrollment. Patients must not be identified by name on any study document. Data will be entered on the CRFs using the unique subject identification number assigned at registration.

All signs, symptoms, HIV-related and AIDS-defining events, toxicities, laboratory results and deaths must be entered on the CRFs. Sample CRFs will be available on the AMC Operations Center website.

### **4.2 Data Submission Schedule - ECOG Institutions**

ECOG Institutions enrolling patients on AMC045 are required to use the AdvantageEDC internet data entry system for the submission of CRFs. Do not use ECOG Forms for this study.

Submissions to QARC for radiation therapy quality control are outlined in [section 5.5.9.6](#).

*Note: It is required that the site obtain instructions and training on the AdvantageEDC system prior to the enrollment of patients onto the trial. Sites may contact the AMC Operations Center via e-mail ([amcpm@emmes.com](mailto:amcpm@emmes.com)) to schedule a training session.*

### **4.3 Role of Data Management**

Instructions concerning the recording of study data on CRFs will be provided by the Operations Center. It is the responsibility of the AMC Operations Center to assure the quality of data for this study. This role extends from protocol development to generation of the final study database.

## 5.0 TREATMENT PLAN

### 5.1 Summary of Treatment Plan

#### 5.1.1 Chemotherapy and Cetuximab (see [sections 5.2–5.4](#))

*Note: All patients will be seen by the radiation oncologist prior to induction chemotherapy. The radiation therapy treatment planning will be based on pre-chemotherapy tumor volumes.*

Chemotherapy will consist of two courses of cisplatin (Days 1 and 29) and 5-FU given for 4 days (i.e., Days 1-4 and 29-32) given concurrently with irradiation. Cetuximab will be also be given concurrently with chemotherapy and radiation. The start date should be a Monday whenever possible so that chemotherapy can overlap with 5 doses of radiation during each cycle. The treatment plan is outlined below:

- Cetuximab is given at a dose of 400 mg/m<sup>2</sup> IV 7 days before the first cisplatin dose and first radiation dose (cycle 1, Day 1), then 250 mg/m<sup>2</sup> on Days 1, 8, 15, 22, 29, 36, and 43. A minimum of 6 and a maximum of 8 doses of cetuximab will be given (including the loading dose). Cetuximab administration may not conform exactly to this treatment schedule if toxicity develops that requires withholding cetuximab because of toxicity related to radiation, cetuximab, chemotherapy, or the combination (see [section 5.4](#) for cetuximab administration guidelines and [sections 7.1–7.2](#) for dose modification). Cetuximab will be given before the cisplatin/5-FU infusion on days when cisplatin is given and/or the 5-FU infusion is initiated.
- 5-FU is given as a 96-hour continuous infusion (generally as an outpatient via a CADD pump and PIC line or Portacath) at a dose of 1000 mg/m<sup>2</sup>/day X 4 days (see [section 5.2](#)). 5-FU will be given on Days 1-4 and Days 29-32 (i.e., begin on the same day of each cisplatin infusion).
- Cisplatin is given at a dose of 75 mg/m<sup>2</sup> IV over 60 minutes on the first day of each course of 5-FU (Day 1 and Day 29) with adequate hydration (3 liters of 0.9% normal saline) (see [section 5.3](#)).
- All patients treated with cisplatin should receive prophylactic antiemetics.
- Chemotherapy and cetuximab dose delay guidelines are described in [section 7.0](#). When there has been a radiation therapy break, the chemotherapy and cetuximab schedule may be affected as described in [section 7.0](#).
- Hypomagnesemia is a known complication of cetuximab and of cisplatin. Patients must be monitored for hypomagnesemia (see [Appendix I](#)), and magnesium supplementation should be administered as clinically indicated at the discretion of the treating physician.

### 5.1.2 Radiation Therapy (see [section 5.5](#))

All patients will be treated with 1.8 Gy per day, 5 days per week for up to 5-6 weeks. IMRT may be used at the discretion of the treating physician according to the guidelines outlined in this protocol.

#### ➤ Primary Tumor

The total dose of irradiation to the primary tumor will be dependent upon T stage:

- T1 or T2 disease: 45 Gy total dose
- T3 or T4 disease or T2 disease with clinical evidence of residual disease after 45 Gy: treat to total dose of between 50.4 Gy – 54.0 Gy

#### ➤ Inguinal Lymph Nodes

The total dose to the inguinal nodes will be dependent upon N stage:

- N0 or N1 (perirectal disease): 30.6 Gy
- N2 or N3: 45 Gy (plus 5.4 – 9.0 Gy to total dose of 50.4 – 54.0 Gy if there is clinical evidence of residual disease after 45 Gy, or for any lymph nodes > 3 cm).

### 5.1.3 Supportive Care

Supportive care measures (antiemetics, anti-diarrhea medicines, narcotics, opportunistic infection prophylaxis) will be given as described in [section 5.5](#) of the protocol. Use of HAART is highly encouraged.

### 5.1.4 Salvage/Secondary Therapy

Patients who relapse, have progressive disease, or who have persistent disease after the completion of protocol therapy may be treated at the discretion of the treating physician, and will be followed for survival.

## 5.2 5-Fluorouracil (5-FU)

### 5.2.1 Formulation, Pharmacology, Supplier, Storage, Potential Toxicity

#### ➤ Dose Formulation

5-FU is available in 10-ml ampules, as a colorless to faint yellow aqueous solution containing 500 mg 5-FU, with pH adjusted to approximately 9.0 with sodium hydroxide. Administration of 5-FU should be only by the intravenous route taking care to avoid extravasation.

#### ➤ Pharmacology

5-FU is a marketed drug available in 500 mg vials. It is a fluorinated pyrimidine belonging to the category of antimetabolites. 5-FU resembles the natural uracil molecule in structure, except that a hydrogen atom has been

replaced by a fluoride atom in the 5 position. There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to the thymidylic acid. In this fashion 5-FU interferes with the synthesis of DNA and to a lesser extent inhibits the formation of ribonucleic division and growth. The effect of fluorouracil may be to create a thymidine deficiency, which provides unbalanced growth and death of the cell. It is primarily metabolized to the inactive dihydro-5-FU by dihydropyrimidine dehydrogenase (DPD) in the liver. Rare patients with DPD deficiency have excessive toxicity following 5-FU. The route of elimination is renal.

➤ Supplier

5-FU is available commercially.

➤ Storage

Although 5-FU solution may discolor slightly during storage, the potency and safety are not adversely affected. Store at room temperature (49°-86° F). Protect from light. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140° F with vigorous shaking; allow it to cool to body temperature before using.

➤ Side Effects and Toxicities

The spectrum of toxicity includes stomatitis and esophagopharyngitis (*which may lead to sloughing and ulceration*), diarrhea with cramping and/or bleeding, anorexia, nausea and emesis are commonly seen during therapy. Leukopenia usually follows every course of adequate therapy with fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first dose, although uncommonly the maximal depression may be delayed for as long as 20 days. By the 30th day the count has usually returned to the normal range. Alopecia and dermatitis may be seen. The dermatitis most often seen is a pruritic maculopapular rash usually appearing on the extremities and less frequently on the trunk. Other side effects include myocardial ischemia, angina, lethargy, malaise, headache, allergic reactions, disorientation, confusion, euphoria, dizziness, incoordination, visual changes, photosensitivity of the eyes and skin, nail changes including loss of nails, skin thickening, cracking, dryness or sloughing, vein pigmentation, biliary sclerosis, or acalculus cholecystitis. Other toxicities included cardiac ischemia, angina, and cardiomyopathy Please refer to the approved package insert for complete prescribing and toxicity.

### 5.2.2 5-FU: Preparation, Dose, Schedule and Administration

The 5-FU can be diluted in D5W or normal saline (NS) to the desired concentration. Diluted solutions are stable for up to 16 weeks if refrigerated. The 5-FU dose is 1000 mg/m<sup>2</sup>/day for 4 days (total dose per cycle is 4000mg/m<sup>2</sup>) given as continuous infusion in 5% D5W or 0.5 NS for 96 hours continuously

starting Day 1. This is to be repeated starting on Day 29. If a patient requires a radiation therapy break for skin toxicity or other reason, chemotherapy should also be delayed. Once radiation is resumed, the chemotherapy should again begin on the first full week so that the 96 hour infusion overlaps with 5 doses of radiation whenever possible. Patients may either be admitted to the hospital for the 5-FU or receive it as an outpatient via a venous access device (such as a PIC line or Porta-Cath) with the use of a pump (i.e., CADD pump). This typically is supplied by a home infusion company and supported by a home nursing agency. The 5-FU is NOT compatible with cisplatin, which should either be given through a separate line or during a brief interruption in the 5-FU infusion.

### 5.3 Cisplatin (CDDP)

#### 5.3.1 Formulation, Pharmacology, Supplier, Storage, Potential Toxicities

##### ➤ Formulation

Cisplatin (*Platinol*) is available as 10 mg and 50 mg vials of dry powder, which are reconstituted with 10 mL, and 50 mL of sterile water for Injection USP, respectively. Cisplatin is also available as a 1-mg/mL solution in 50 and 100 mg vials.

##### ➤ Pharmacology

This atypical alkylating agent's dominant mode of action appears to involve the formation of a bifunctional adduct resulting in DNA crosslinks. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 18 to 37 minutes, and a secondary phase ranging from 44 to 190 hours. This prolonged phase is due to protein binding, exceeding 90%. Urinary excretion is incomplete with only 27 to 45% excreted in the first 5 days. The initial fractions are largely unchanged drugs.

##### ➤ Supplier

Cisplatin is available commercially.

##### ➤ Storage

The intact vials should be stored at room temperature.

##### ➤ Side Effects and Toxicity

Include anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient), neurotoxicity (may be severe and irreversible), ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus), hyperuricemia, magnesium and potassium wasting, seizures, rash, ocular toxicities, rare cardiac abnormalities, or possible acute myeloid leukemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretion.

Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about 2 weeks with recovery generally at about 3 weeks after the initiation of therapy. Rare complications are loss of taste, allergic reactions, loss of muscle or nerve function, and vascular complications. Please refer to the approved package insert for complete prescribing and toxicity.

### 5.3.2 Cisplatin: Preparation, Schedule, and Administration

#### ➤ Preparation

The intact vials should be stored at room temperature. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. Due to a lack of preservatives, the solution should be given immediately after preparation, or at least within eight hours of reconstitution, as a slow intravenous infusion. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D5-1/2NS (precipitation occurs in D5W). Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes. Cisplatin is incompatible with 5-FU, and thus it should either be given through a separate line or during a brief break in the 5-FU infusion.

The CDDP dose is 75 mg/m<sup>2</sup> in 250 mL NS intravenous infusion over a minimum of 60 min on the first day of each 5-FU infusion (Days 1 and 29). If required, the CDDP can be given another day during the week of 5-FU (i.e., for a Monday holiday or another scheduling reason). The CDDP may be given in either an outpatient infusion center or hospital setting. It must be given on a day that radiation therapy and 5-FU are to be given. Patients should receive up to 2,000 mL of an IV physiologic fluid prior to cisplatin therapy. This may be accomplished in the hours prior to dose administration or more gradually beginning the previous evening. Post-cisplatin IV hydration of at least 1,000 mL of physiologic solution containing potassium and magnesium supplementation may follow. Patients should be recommended to drink generous amount of liquids orally before and after cisplatin therapy (suggested volume is 2L).

## 5.4 Cetuximab

#### ➤ Description

Cetuximab is an anti-EGFR human-to-murine chimeric antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment and nanofiltration. Cetuximab is not known to be a vesicant.



➤ Supplier/How Supplied

Bristol-Myers Squibb (BMS) will supply cetuximab free of charge to the patient. The product is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Each single-use 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42mg/mL sodium phosphate monobasic monohydrate, and Water for injection, USP.

➤ Packaging and Labeling

Cetuximab for injection will be supplied by BMS in single-use, ready-to-use 50-mL vials containing 2 mg/mL of product.

➤ Handling and Dispensing

Cetuximab must be dispensed only from official study sites by authorized personnel according to local regulations. Cetuximab should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that study drug is only dispensed to study patients.

➤ Storage Requirement/Stability

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). DO NOT FREEZE. Increased particulate formation may occur at temperatures at or below 0° C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

➤ Preparation and Administration Techniques

Cetuximab must NOT be administered as an IV push or bolus. Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. DO NOT SHAKE OR DILUTE.

Cetuximab can be administered via infusion pump or syringe pump.

➤ Infusion Pump

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).

2. Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (e.g., Baxter Intravia), ethylene vinyl acetate bags (e.g., Baxter Clintec), DEHP plasticized PVC bags (e.g., Abbott Lifecare), or PVC bags.
3. Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
4. Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
5. Affix the infusion line and prime it with cetuximab before starting the infusion.
6. Maximum infusion rate should not exceed 5 mL/min.
7. Use 0.9% saline solution to flush line at the end of infusion.

➤ **Syringe Pump**

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
2. Place the syringe into the syringe driver of a syringe pump and set the rate.
3. Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
4. Connect up the infusion line and start the infusion after priming the line with cetuximab.
5. Repeat procedure until the calculated volume has been infused.
6. Use a new needle and filter for each vial.
7. Maximum infusion rate should not exceed 5 mL/min.
8. Use 0.9% saline solution to flush line at the end of infusion.

Cetuximab should be piggybacked to the patient's infusion line.

Following the cetuximab infusion, a 1-hour observation period is recommended.

➤ **Safety Precautions**

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provided documented procedures for destruction are in place.

Cetuximab therapy should be used with caution in patients with known hypersensitivity to Cetuximab, murine proteins, or any component of this product. It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

#### 5.4.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Cetuximab (NSC 714692)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/aeguidelines.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) for further clarification. *Frequency is provided based on 2282 patients.* Below is the CAEPR for Cetuximab.

Version 2.1, March 31, 2010<sup>1</sup>

Adverse Events with Possible Relationship to Cetuximab (CTCAE 4.0 Term) [n= 2282]			EXPECTED AEs FOR CTEP-AERS REPORTING Agent Specific Adverse Event List (ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	<i>Expected</i>
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
EAR AND LABYRINTH DISORDERS			
	External ear inflammation		
	Tinnitus		
EYE DISORDERS			
	Conjunctivitis		<b><i>Conjunctivitis</i></b>
	Dry eye		<b><i>Dry eye</i></b>
	Uveitis		<b><i>Uveitis</i></b>
	Watering eyes		<b><i>Watering eyes</i></b>
GASTROINTESTINAL DISORDERS			
	Abdominal pain		<b><i>Abdominal pain</i></b>
	Cheilitis		<b><i>Cheilitis</i></b>
	Constipation		<b><i>Constipation</i></b>
Diarrhea			<b><i>Diarrhea</i></b>
	Dry mouth		<b><i>Dry mouth</i></b>
	Dyspepsia		<b><i>Dyspepsia</i></b>
	Mucositis oral		<b><i>Mucositis oral</i></b>
Nausea			<b><i>Nausea</i></b>
	Vomiting		<b><i>Vomiting</i></b>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		<b><i>Chills</i></b>
	Edema limbs		
Fatigue			<b><i>Fatigue</i></b>

Adverse Events with Possible Relationship to Cetuximab (CTCAE 4.0 Term) [n= 2282]			EXPECTED AEs FOR CTEP-AERS REPORTING Agent Specific Adverse Event List (ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	Expected
Fever			<i>Fever</i>
	Flu like symptoms		<i>Flu like symptoms</i>
	Infusion related reaction		<i>Infusion related reaction</i>
	Non-cardiac chest pain		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		<i>Allergic reaction</i>
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection <sup>2</sup>		
		Infections and infestations – Other (aseptic meningitis)	
INVESTIGATIONS			
	Neutrophil count decreased		
	Weight loss		<i>Weight loss</i>
	White blood cell decreased		<i>White blood cell decreased</i>
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		<i>Anorexia</i>
	Dehydration		<i>Dehydration</i>
	Hypocalcemia		
	Hypomagnesemia		<i>Hypomagnesemia</i>
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		<i>Arthralgia</i>
	Back pain		<i>Back pain</i>
	Myalgia		<i>Myalgia</i>
NERVOUS SYSTEM DISORDERS			
Headache			<i>Headache</i>
	Syncope		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		<i>Allergic rhinitis</i>
	Bronchospasm		
	Cough		<i>Cough</i>
	Dyspnea		<i>Dyspnea</i>
	Hoarseness		<i>Hoarseness</i>
		Pneumonitis	
		Respiratory, thoracic, and mediastinal disorders - Other (non-cardiogenic pulmonary edema)	

Adverse Events with Possible Relationship to Cetuximab (CTCAE 4.0 Term) [n= 2282]			EXPECTED AEs FOR CTEP-AERS REPORTING Agent Specific Adverse Event List (ASAEI)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	Expected
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		<i>Alopecia</i>
Dry skin			<i>Dry skin</i>
	Nail loss		<i>Nail loss</i>
		Palmar-plantar erythrodysesthesia syndrome	
	Photosensitivity		<i>Photosensitivity</i>
	Pruritus		<i>Pruritus</i>
	Purpura		
Rash acneiform			<i>Rash acneiform</i>
Rash maculo-papular			<i>Rash maculo-papular</i>
	Skin ulceration		
	Urticaria		<i>Urticaria</i>
VASCULAR DISORDERS			
	Hypotension		<i>Hypotension</i>
	Thromboembolic event		<i>Thromboembolic event</i>

<sup>1</sup>This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting **PIO@CTEP.NCI.NIH.GOV**. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

<sup>2</sup>Infection could include all 75 sites of infections under the INFECTIONS AND INFESTATIONS SOC.

**Also reported on cetuximab trials but with the relationship to cetuximab still undetermined:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Disseminated intravascular coagulation; Hemolysis

**CARDIAC DISORDERS** - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Left ventricular systolic dysfunction; Myocardial infarction; Paroxysmal atrial tachycardia; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

**EAR AND LABYRINTH DISORDERS** - Hearing impaired

**EYE DISORDERS** - Blurred vision; Extraocular muscle paresis; Eyelid function disorder; Keratitis; Photophobia; Vitreous hemorrhage

**GASTROINTESTINAL DISORDERS** - Colitis; Dysphagia; Esophagitis; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal hemorrhage (including Colonic or Gastric hemorrhage or hemorrhage in other sites under the GASTROINTESTINAL DISORDERS SOC); Gastrointestinal perforation (Colonic perforation, Duodenal perforation, or

perforation in other sites under the GASTROINTESTINAL DISORDERS SOC); Gastrointestinal ulcer (ulcer includes Duodenal ulcer, Rectal ulcer, or ulcer in other sites under the GASTROINTESTINAL DISORDERS SOC); Ileus; Pancreatitis; Rectal fistula

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Edema face; Sudden death NOS

**HEPATOBIILIARY DISORDERS** - Cholecystitis; Hepatic failure

**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Bruising; Wound dehiscence

**INVESTIGATIONS** - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; Platelet count decreased; Serum amylase increased

**METABOLISM AND NUTRITION DISORDERS** - Hyperkalemia; Hyperuricemia; Hypokalemia; Hyponatremia; Hypophosphatemia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (myasthenia); Musculoskeletal and connective tissue disorder - Other (Sudeck's Atrophy)

**NERVOUS SYSTEM DISORDERS** - Ataxia; Dizziness; Dysgeusia; Extrapyrimal disorder; Intracranial hemorrhage; Nervous system disorders - Other (cholinergic syndrome); Neuralgia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Tremor

**PSYCHIATRIC DISORDERS** - Agitation; Depression

**RENAL AND URINARY DISORDERS** - Hematuria; Renal and urinary disorders - Other (acute renal failure)

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Reproductive system and breast disorders - Other (balanitis); Vaginal inflammation

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Atelectasis; Bronchopulmonary hemorrhage; Epistaxis; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans-organized pneumonia [BOOP])

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Hirsutism; Skin hypopigmentation; Skin and subcutaneous tissue disorders - Other (skin fissures)

**VASCULAR DISORDERS** - Flushing; Hypertension; Lymphedema; Vasculitis

**Note:** Cetuximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

➤ Cetuximab Administration

All patients should be premedicated with diphenhydramine hydrochloride 50 mg (or an equivalent antihistamine) by IV given 30-60 minutes prior to the first dose of cetuximab. Premedication may be administered prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine (or a similar agent) may be reduced.

The initial dose of cetuximab is 400 mg/m<sup>2</sup> intravenously administered over 120 minutes, followed by weekly infusions at 250 mg/m<sup>2</sup> IV over 60 minutes. The infusion rate of cetuximab must never exceed 5 mL/min. Patients must be continuously observed during the infusion for signs of anaphylaxis.

Patients will be closely monitored for treatment-related AEs, especially infusion reactions (see [section 5.2.1](#)), during the infusion and the post-infusion observation hour. For the initial cetuximab infusion, vital signs should be monitored pre-infusion, 1/2 hour into the infusion, at the end of the infusion and 1 hour post-infusion. For subsequent infusions, vital signs should be taken pre- and post-infusion; however, it is recommended that the patient be observed for 1 hour post infusion.

For the duration that patients are on study therapy, AE monitoring will be done continuously. Patients will be evaluated for AEs at each visit and are to be instructed to call their physician to report any clinically significant AEs between visits.

**Drug Ordering and Accountability:** Following submission and approval of the required regulatory documents, a supply of cetuximab may be ordered from BMS. Please find the Cetuximab (Erbix<sup>TM</sup>) Request for Drug Shipment form on the AMC Operations Center website ([www.amcoperations.com](http://www.amcoperations.com)). Quantities must be ordered in multiples of four (keeping in mind that you will need 7-9 vials for an initial dose, and 4-6 vials for weekly maintenance doses, dependent on patient's BSA). A suggested initial shipment is 20 vials. Allow 5 business days for shipment of drug from receipt of the C225 (Cetuximab) Clinical Supply Shipment Request form. The Drug Supply Shipment Form can be downloaded from the AMC Operations Center website in MS Word format.

All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from BMS on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs. Protocol specific stickers will be provided to the sites for placement on the vials during drug check-in. It is possible that sites may have more than one cetuximab clinical study ongoing at the same time. It is imperative that only product designated for AMC-045 be utilized for this study.

Inside each shipping container will be a disposable electronic unit (TagAlert<sup>TM</sup>) to ensure the product has remained at the appropriate temperature during shipping. This unit will be attached to an information card. The LCD display will show OK (indicating no alarm has been triggered) or a black bar and the number(s) 1-4 (indicating an alarm/alerts have been triggered). Should an alarm be triggered, follow the instructions on the attached information card. Display results should be recorded on the packing

list. For questions regarding drug requisitioning contact BMS at 800 743-9224.

**Important Reorder Instructions:** Reorders should be emailed directly to BMS using **cetuximab.drug@bms.com** or via fax at 609 252-7856 for shipment within 5 days.

When assessing need for re-supply, institutions should keep in mind the number of vials used per treatment dose (~7-9 for initial dose, ~4-6 for weekly maintenance doses, dependent on patient's BSA), and that shipments may take 5 business days from BMS receipt of request. Quantities must be in multiples of four.

**Receipt of Drug Shipment:** Study drug shipments will include a TagAlert™ unit and attached information card (see above for description) and a clinical supply packing list (CSPL). The pharmacist/study personnel responsible for the clinical study product will need to indicate the condition of the shipment, record the TagAlert™ results, and sign the CSPL in the designated areas. The pharmacist/study personnel will keep a photocopy for the site's records, and return the original to BMS, using the enclosed, pre-addressed envelope. The TagAlert™ unit can be discarded after the reading is recorded on the CSPL.

**At the Completion of the Study:** At the completion of the infusion all open study drug should be destroyed according to institution policy. At the end of the study, all unused drugs will be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

## **5.5 Radiation Therapy**

All patients will be treated with 1.8 Gy per day, 5 days per week. Treatment breaks will only be allowed for toxicity. Dose adjustments for toxicity are discussed in [section 7.0](#). There will be no scheduled breaks. Patients should receive their chemotherapy concurrently. If a patient is on a break for skin toxicity, the chemotherapy and cetuximab should be delayed until radiation therapy resumes. Patients should be seen and examined weekly to monitor tolerance to treatment, skin toxicity, and tumor response. Supportive care should be provided as appropriate.

### **5.5.1 Standard Radiation Therapy Doses**

All patients will be treated with a daily dose of 1.8 Gy, 5 days per week, to a dose of 45 Gy in 25 fractions over 5 weeks. There are no scheduled treatment breaks. Treatment breaks of < 10-days will only be allowed for severe toxicity; dose adjustments for toxicity are discussed in [section 7.0](#).

Patients with T3, T4, or N+ lesions, or T2 lesions with clinical evidence of residual disease after 45 Gy, may receive an additional 5.4 – 9.0 Gy (1.8 Gy per



fraction) to a reduced field, per the treating radiation oncologist's discretion. A further radiation boost is discouraged, and must be discussed with the protocol chairs.

Patients with N0 disease or patients with N1 disease (perirectal only involvement) will receive 30.6 Gy electively to the bilateral inguinal fossa. For patients with inguinal or pelvic metastases, or for lymph nodes greater than 3 cm, the entire metastatically involved nodal region is to be included to 45 Gy, and further boost irradiation of 5.4-9 Gy may be given for residual nodal disease as outlined in [Section 5.5.3](#).

#### 5.5.2 Standard Radiation Simulation/Equipment

Treatment for patients must be planned on a simulator, which exactly reproduces the geometry of the treatment machine and is capable of producing diagnostic quality radiographs. Patients are to be simulated in the supine or prone position. A radio-opaque marker should be placed over the anus or the most caudal extent of the tumor, whichever is most inferior. Small bowel contrast should be administered approximately one hour prior to simulation.

Patients must be treated with radiotherapy equipment with photon energy of 6 MV or greater for pelvic fields with minimum target/axis distance (TAD of 100 cm). Supplementary inguinal node irradiation (see [section 5.5.3](#)) is to be given preferably by electrons (low energy photons are allowed at Investigator's discretion).

Three-dimensional treatment planning is allowed.

#### 5.5.3 Standard Radiation Treatment Fields

##### ➤ Initial Pelvic Fields

Patients will receive 30.6 Gy at 1.8 Gy/day with bladder distended. All fields should receive radiation daily. The pelvis, anus, perineum, and bilateral inguinal lymph nodes will be treated with AP-PA fields, 3-field or a 4-field technique. If a 3 or 4-field technique is used, the inguinal nodes should not be included in the lateral fields.

The superior border of this initial pelvic field shall be the L5-S1 interspace. The inferior border shall include the anus with a minimum margin of 2.5 cm around the anus and inferior extent of the tumor. The lateral border of the AP/PA field shall include the lateral inguinal nodes as determined by bony landmarks or lymphangiogram. If the Investigator chooses not to include the lateral extent of the inguinal fossa in the PA field, then the inguinal nodes are to be boosted with electrons ([section 5.5.3](#)) and the lateral border of the PA field shall extend 2 cm lateral to the greater sciatic notch. If a 3-4 field technique is utilized, the target volume includes all areas at risk (pelvis, anus plus margin, inguinal nodes, external iliac nodes). A CT or lymphangiogram

should be used to construct nodal volumes. Inguinal nodes must not be underdosed (see Inguinal Field section below).

*Note: If the patient has a CD4 count less than 200, then the reduced pelvic field #2 or PTV 2 may be used for the entire treatment course.*

➤ **Reduced Pelvic Field #1**

After 30.6 Gy has been given to the initial pelvic field, the superior border shall be dropped to the upper level of the greater sciatic notch (inferior border of SI joints). The reduced pelvic field shall be continued to 39.6 Gy at 1.8 Gy per day.

For patients with CD4 counts of < 200, reduced pelvic field # 2 should be used after 30 Gy.

➤ **Reduced Pelvic Field #2**

After 39.6 Gy, boost fields shall be utilized to encompass the original primary tumor volume plus a 2.0 to 2.5 cm margin. Treatment field options include reduced multiple photon fields with the patient in supine position (i.e., 4-field or PA and laterals with wedges) or a direct photon or electron perineal field with the patient in the lithotomy position. All patients shall receive 5.4 Gy (total 45 Gy) with this boost.

Patients with T3, T4, or N+ lesions, or T2 lesions with residual disease after 45 Gy, may receive an additional 5.4-9 Gy (total 50.4-54 Gy) with this reduced field, per the treating radiation oncologist's discretion. Further radiation boosts are discouraged, and must be discussed with the protocol chairs.

If pelvic nodes are grossly involved, they should be included in the final boost field if small bowel can be avoided. Of note, all small bowel should be excluded from the treatment field after 50.4 Gy.

➤ **Inguinal Fields**

All patients shall receive elective inguinal node irradiation. The initial AP pelvic field should be designed to include the entire inguinal region along with the pelvis; the PA field may or may not include the lateral inguinal region, (as per the discretion of the Investigator).

Patients with N0 disease or patients with N1 disease (perirectal only involvement) will receive 30.6 Gy at a minimum depth of 3 cm from the anterior surface (use CT or lymphangiogram to calculate the depth). If lateral inguinal nodes are not covered by the PA photon field, supplementary RT will be delivered with anterior electron fields to the lateral inguinal region which

are matched with the exit PA field; the boost may be given with low energy photons if electron beam is not available.

In patients with involved inguinal nodes not completely included within the idealized pelvic AP photon field, the treatment volume is to be extended as needed to provide a minimum 2-cm margin around all palpable and radiographic metastatic disease.

For patients with inguinal metastases the entire metastatically involved inguinal region is to be included to 45 Gy. Further boost irradiation (5.4-9 Gy in 1.8 Gy fractions) may be administered to the tumor plus 2.0-2.5 cm margin for residual disease, or for lymph nodes greater than 3 cm, per the discretion of the treating radiation oncologist.

Pelvic lymph node metastases will require photon therapy to include the primary tumor along with nodal disease. Inguinal lymph node metastases will require carefully planned electron fields (low energy photons may be used if electrons are not available).

#### 5.5.4 Standard Radiation Dose Specifications

##### ➤ Photon Beams

- a) For two opposed coaxial equally weighted beams: on the central ray at mid separation of beams.
- b) For an arrangement of two or more intersecting beams: at the intersection of the central rays of beams.
- c) For two opposing coaxial unequally weighted beams: on the central ray at the center of the target area.
- d) Other or complex treatment arrangements: at the center of the target area (Note: there may be several target areas).
- e) Off axis calculation at the level of the primary tumor is required.

##### ➤ Electron Beams:

- a) The target dose shall be prescribed at the depth of maximum dose.
- b) The energy and field size shall be chosen so that the target volume is encompassed within 90% of the prescribed dose.
- c) The maximum or minimum acceptable dose variation across the tumor volume is  $\pm 10\%$  of the maximum dose at central axis.

##### ➤ Inguinal Node Fields

The daily dose, at the appropriate depth specified below, shall be 1.8 Gy. The total dose at this depth shall be 30.6 Gy for N0 patients or patients with N1 disease (perirectal only involvement) or 45 Gy for N+ patients, and 50.4-54 Gy for patients with residual inguinal metastases after 45 Gy or for lymph

nodes greater than 3 cm. In N0 or NI patients, the dose shall be specified at a minimum depth of 3-cm (use CT or lymphangiogram for exact depth). If electrons are used, energy is to be selected so that the dose at dmax is no more than 10% greater than the dose at prescription depth. In patients with metastatically involved inguinal lymph nodes, the dose shall be specified on the central axis at the deepest portion of metastatically involved tumor. If electrons are used, energy is to be selected so that the dose at dmax is no more than 10% greater than the dose at the specified prescription depth.

#### 5.5.5 IMRT and 3D Conformal Planning Guidelines

Because of the potential advantages of IMRT, this protocol allows use of both standard and conformal planning techniques. For conformal techniques, approved benchmarks must be on file at QARC. Centers participating in this protocol using 3D conformal techniques are required to complete the 3D Benchmark; those treating with IMRT must complete the IMRT Questionnaire and either the QARC Benchmark or irradiate the RPC's IMRT head and neck phantom. The Benchmark material can be obtained from the Quality Assurance Review Center ([www.QARC.org](http://www.QARC.org)). Contact the RPC (<http://rpc.mdanderson.org/rpc>) for information regarding their IMRT phantoms.

The radiation oncologist prior to induction chemotherapy will see all patients. The radiation therapy treatment planning will be based on pre-chemotherapy tumor volumes. Treatment breaks will only be allowed for toxicity. Dose adjustments for toxicity are discussed below. There will be no scheduled breaks. Treatment breaks of < 10-days will only be allowed for severe toxicity. Patients should receive their chemotherapy concurrently. If a patient is on a break for skin toxicity, the chemotherapy and cetuximab should be held until radiation therapy resumes. Patients should be seen and examined weekly to monitor tolerance to treatment, skin toxicity, and tumor response. Supportive care should be provided as appropriate.

#### 5.5.6 IMRT Equipment

- Modality: Linear accelerator-based photons with a minimum energy of 6 MV will be used. Electrons may be used in the elective treatment of inguinal nodes at the discretion of the attending radiation oncologist.
- Geometry: Teletherapy units with a source-to-axis distance greater than or equal to 80 cm.
- Calibration: Teletherapy units used in this study shall have their calibration verified by the Radiological Physics Center (RPC).

#### 5.5.7 IMRT and 3D Conformal Planning Target Volume Definitions

ICRU 50 and ICRU 62 prescription methods and nomenclature shall be utilized for this study. This will apply to both conformal and non-conformal techniques. The volumes are to be defined by planning CT techniques. There are two treatment volumes: an initial volume (PTV1) and a boost (PTV2).

➤ Gross Tumor Volume (GTV)

This is defined as all known gross disease determined from the digital rectal examination, proctoscope and CT (and MRI or PET if performed), including the gross primary anal tumor volume and any enlarged ( $\geq 1$  cm on imaging) or biopsy positive peri-rectal, iliac or inguinal nodes.

➤ Clinical Target Volume 1 (CTV 1)

This is defined as the GTV with a 2-cm. margin, plus areas considered containing potential microscopic disease. The CTV for this study should include the pre-sacral space with the superior boundary at the sacral promontory, the mesorectum, the right and left inguinal fossa, the right and left internal iliacs, and the right and left external iliacs. The cephalad (superior) border of the treatment volume shall be at or above S2 but not beyond L5/S1. The caudad (inferior) border of the treatment volume shall attempt to exclude the lateral perineal skin. The elective nodal regions will be contoured based on the elective lymph node contouring guidelines of RTOG (<http://www.rtog.org/anoratl/main.html>). For contouring of elective inguinal lymph node region, a 1.5 cm margin on contrast enhanced femoral vessels extending from the level of top of the femoral heads to bottom of the ischial tuberosity will be used. Care should be taken to ensure adequate coverage of the mesorectum and presacral area as outlined by the atlas, as well as manually trimming the CTV off nontarget muscle, bone and small bowel.

➤ Planning Target Volume 1 (PTV 1)

Initial Planning Target Volume (PTV1): For the purpose of this study, a margin for set up error and/or patient motion is to be added to the CTV. Depending upon the immobilization methods and patient cooperation, this may vary but must be at least 1 cm. Exact margins will be left to the discretion of the treating radiation oncologist and do not have to be uniform in all dimensions. A nodal PTV should not be allowed to overlap with the primary PTV, provided that their dose objectives are different, so that the maximum dose to the nodal PTV can be controlled in the optimization.

➤ Clinical Target Volume 2 (CTV 2)

This is defined as the GTV only with a 2 cm margin.

➤ Planning Target Volume 2 (PTV 2)

This is defined as the CTV 2 with at least a 1 cm margin.

After 39.6 Gy in 1.8 Gy Monday through Friday daily fractions to the PTV 1, boost fields shall be utilized to treat the GTV alone (PTV 2). All patients shall receive 5.4 Gy (total 45 Gy) with this boost.

Patients with T3, T4, or N+ lesions, or T2 lesions with residual disease after 45 Gy, may receive an additional 5.4-9 Gy (total 50.4-54 Gy) to PTV2, per the treating radiation oncologist's discretion. Further radiation boosts are discouraged, and must be discussed with the protocol chairs. If pelvic or inguinal nodes are grossly involved, they should be included in PTV2 if small bowel can be avoided. Of note, all small bowel should be excluded from the treatment field after 50.4 Gy.

#### 5.5.8 IMRT/3D Conformal Target Dose

➤ Prescription Point

The prescription point for each target volume is at or near the center of the target volume. For 3D conformal planning and IMRT dose may be prescribed to an isodose surface provided that the dose uniformity requirements below are satisfied.

➤ Dose Definition

Dose is to be specified in cGy to muscle.

➤ Tissue Heterogeneity

Calculations that take into account tissue heterogeneities are required for all CT-based planning techniques.

➤ Prescription Dose and Fractionation

All patients are to receive a minimum dose of 4500 cGy to the GTV. The prescription is as follows:

- PTV1: The total dose will be 3960 cGy in 22 fractions.
- PTV2: The cumulative dose within the boost volume shall be 4500 cGy.

For patients with T3, T4, or N+ lesions, or T2 lesions with residual disease after 45 Gy, an additional 5.4-9 Gy (total 50.4-54 Gy) may be delivered to PTV2, per the treating radiation oncologist's discretion.

*Note: If the patient has a CD4 count of less than 200, then the PTV 2 may be used for the entire treatment course.*

➤ Dose Uniformity

The PTV should receive +10/-5% of the prescribed dose. For 3D conformal and IMRT planning this may be interpreted as requiring that at least 95% of the PTV or should be encompassed within the 95% isodose surface and no more than 5% of the PTV should receive greater than 110% of the prescription dose as evaluated by DVH.

## 5.5.9 IMRT Time-Dose Considerations

### ➤ Daily Dose

The daily dose to the prescription point of the original and boost volumes shall be 180 cGy.

### ➤ Fractionation

Treatment shall be given 5 days per week. All radiation fields shall be treated daily.

### 5.5.9.1 IMRT Treatment Technique

This study allows both standard and conformal planning techniques. Conformal planning techniques are encouraged. IMRT is allowed.

### ➤ Simulation

Patients should be planned using a CT simulator, or on a simulator, which exactly reproduces the geometry of the treatment machine and is capable of producing diagnostic quality radiographs. Conformal simulation will be done with the patient in the supine "arms up" or prone "arms up" position using a CT-simulator with a slice thickness  $\leq 5$  mm. A custom immobilization device (such as Alpha Cradle for supine patients and an Alpha Cradle with bowel displacement device for prone patients) is suggested to minimize set-up variability. Oral and IV CT contrast is recommended, as is air in the rectum. Of note, daily portal imaging is strongly encouraged for patients being treated in the prone position on a bowel displacement device. Additionally, consideration should be given to using the lightest couch top available to avoid unnecessary bolus effect. A radio-opaque marker, should be placed over the anus or the most caudal extent of the tumor, whichever is most inferior. Small bowel contrast should be administered approximately one hour prior to simulation. Target tumor volumes are delineated slice by slice on the treatment planning CT images.

### 5.5.9.2 IMRT Normal Tissue Sparing

### ➤ Critical Normal Structures

The PTVs should spare non-target skin surfaces (manually or automatically trimmed to 3-5mm within the skin surface). In addition, surrounding critical normal structures, including the femoral heads (right and left), bladder, external genitalia, iliac crest, small bowel, large bowel outside the CTVs, and perianal skin should be outlined. The normal tissues will be contoured and considered as solid organs. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified

tissue. DVHs must be generated for all critical normal structures. Effort should be made to achieve the listed dose constraints to normal tissues below, as follows. NOTE: They are listed in order from most to least important.

- Small Bowel
  - No more than 200 cc above 30 Gy
  - No more than 150 cc above 35 Gy
  - No more than 20 cc above 45 Gy
  - None above 50 Gy
- Femoral Heads
  - No more than 50% above 30 Gy
  - No more than 35% above 40 Gy
  - No more than 5% above 44 Gy
- Iliac Crests
  - No more than 50% above 30 Gy
  - No more than 35% above 40 Gy
  - No more than 5% above 50 Gy
- External Genitalia
  - No more than 50% above 20 Gy
  - No more than 35% above 30 Gy
  - No more than 5% above 40 Gy
- Bladder
  - No more than 50% above 35 Gy
  - No more than 35% above 40 Gy
  - No more than 10% above 50 Gy
- Large Bowel
  - No more than 200 cc above 30 Gy
  - No more than 150 cc above 35 Gy
  - No more than 20 cc above 45 Gy

#### 5.5.9.3 IMRT/3D Conformal Planning Dose Calculation and Reporting

- Monitor Unit Calculations

Computer printouts used to determine monitor unit settings to deliver the prescribed dose shall be submitted. If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA



phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.

➤ Dose Uniformity

The maximum and minimum doses in the PTV shall be calculated and reported. These may be extracted from isodose distributions, calculated separately or derived from DVHs.

➤ Critical Organs

The daily dose to the critical organs indicated in [Section 5.5.9.2](#) shall be calculated whenever they are included in the radiation therapy treatment field. These doses must be recorded in the treatment records and submitted with the QA documentation. For patients treated with volume-based techniques, the appropriate dose volume histograms shall be submitted.

➤ Isodose Distributions

A hard copy isodose distribution for the total dose plan in the axial, sagittal, and coronal planes, which includes the isocenter of the planning target volume (PTV) must be submitted. If sagittal and coronal planes are not available, then five axial distributions may be submitted (central axis, two superior and two inferior planes). These dose distributions must include a sufficient number of isodose contours should be shown to determine that the dose distribution conforms to the protocol guidelines. These isodoses should be superimposed over treatment planning CT or MR images.

➤ Conformal Volume Contouring

CT submission of GTV, CTV1, PTV1, CTV2, PTV2, Small Bowel, on all planning slices must be submitted in patients receiving conformal therapy.

#### 5.5.9.4 IMRT/3D Conformal Planning QA Documentation

Please refer to the QARC Submission Schedule for Radiation Materials found on page 39 for an itemized list of submission materials and instructions regarding the timing of submissions.

- These data should be forwarded to:

Quality Assurance Review Center  
272 West Exchange Street, Suite 101  
Providence, Rhode Island 02903-1025  
Phone: 401-454-4301  
Fax: 401-454-4683

- Questions regarding the dose calculations or documentation should be directed to:

Protocol Dosimetrist  
Quality Assurance Review Center  
272 West Exchange Street, Suite 101  
Providence, Rhode Island 02903-1025  
Phone: 401-454-4301  
Fax: 401-454-4683

- Questions regarding the radiotherapy section of this protocol should be directed to:

Madhur Garg, MD, Email: [mgarg@montefiore.org](mailto:mgarg@montefiore.org) or  
Lisa Kachnic, MD, Email: [Lisa.Kachnic@bmc.org](mailto:Lisa.Kachnic@bmc.org)

#### 5.5.9.5 Definitions of Deviations in Protocol Performance

##### ➤ Prescription Dose

##### PTVs (primary or nodal)

- Minor Deviation: The dose to the prescription point differs from that in the protocol by between 6% and 10%
- Major Deviation: The dose to the prescription point differs from that in the protocol by more than 10%

##### Small Bowel

- Minor deviation: 150-300 cc above 35 Gy, or 20-30 cc above 45 Gy
- Major deviation:  $\geq 300$  cc above 35 Gy, or  $\geq 30$  cc above 45 Gy

##### Femoral Heads

- Minor deviation: 5-10% above 44 Gy
- Major deviation:  $\geq 10\%$  above 44 Gy

##### Dose Uniformity

- Minor Deviation: The variation of dose in one of the target volumes exceeds the limits specified in [section 5.5.8](#).

##### Volume

- Minor Deviation: Margins less than specified or fields excessively large as deemed by the study.
- Major Deviation: Transection of tumor (GTV) or potentially tumor bearing area (CTV).

#### 5.5.9.6 Monitoring of Radiation

- Patients are to be seen and status checked at least once weekly with notation of weight, primary tumor status, skin toxicity, and tolerance to treatment (see [section 6.2](#)).
- Blood counts are to be checked weekly during radiation therapy.
- Criteria for dose modifications/delays of radiation therapy are outlined in [section 7.0](#). Questions regarding radiation therapy may be addressed to the radiation oncology protocol co-chair (Lisa S. Kachnic, MD, see Protocol Roster for contact information).
- Radiation therapy quality control will be performed by the Quality Assurance Review Center (QARC). All radiotherapy quality assurance materials should be submitted to QARC using the schedule outlined below:

#### QARC Submission Schedule for Radiation Materials

Radiation Oncology Materials	QARC Submission Schedule
<p>Copies of the planning CT and the diagnostic imaging utilized in defining the gross target volume.*</p> <p>Copies of simulator films and /or digitally reconstructed radiographs (DRRs) for each field. It is strongly encouraged that the GTV, CTV and PTV1, PTV2 be drawn on the simulator films.</p> <p>Prescription sheet for ENTIRE treatment.</p> <p>Partial Daily Treatment record.</p> <p>First day portal films (or hard copy of real time portal images) if achievable.</p> <p>Photographs of the patient in the treatment position with the fields marked.</p> <p>Completed RT-1 form or IMRT Dosimetry Summary Form (These can be found at <a href="http://www.qarc.org">www.qarc.org</a>).</p> <p>Copies of Beam's eye views with target and critical structures displayed (if 3D conformal planning is used).</p> <p>Documentation of an independent check of the calculated dose (if IMRT is used).</p> <p>One set of orthogonal anterior/posterior and lateral films for isocenter localization for each group of concurrently treated beams. If portals being submitted contain an orthogonal set, this is sufficient.</p> <p>Copies of worksheets and /or printouts used for calculations of monitor units.</p> <p>Copies of composite isodose distributions to demonstrate that the dose variation is within specification. The target volume and the prescription point must be clearly shown.**</p> <p>Dose volume histograms for the PTV and critical structures listed in <a href="#">section 5.5.9.2</a> for the composite</p>	<p>Within <b>3 days</b> of the beginning of Radiation Therapy, the following data shall be submitted.</p> <p>*Submission of Diagnostic Imaging data in digital format is preferred over films. Digital files must be in Dicom format. These files can be burned to a CD and mailed to QARC. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD.</p> <p>Planning CTs with structures can be submitted in RTOG or DicomRT format. For more information about digital data submissions, please visit <a href="http://www.qarc.org">www.qarc.org</a>.</p> <p>**Black and white copies of color documentation are not acceptable.</p>

Radiation Oncology Materials	QARC Submission Schedule
<p>plan (for CT-based planning).</p> <p>Dose volume histogram for “unspecified tissue,” which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure (for IMRT).</p>	
<p>Copies of additional simulation and verification (portal) films for any field modifications made subsequent to the initial reporting of data for on-treatment review.</p> <p>A copy of the patient’s radiotherapy completed daily treatment record.</p> <p>Copies of calculations and isodoses performed subsequent to the submission of the initial data.</p> <p>Completed RT-2 form (This can be found at <a href="http://www.qarc.org">www.qarc.org</a>).</p>	<p>Within one week of the completion of radiotherapy, the following data shall be submitted.</p>

## 5.6 Concurrent Medications

- Some of the agents used in this trial may have an overlapping toxicity profile with antiretroviral agents and other agents commonly used in the management of patients with advanced HIV infection (e.g., neurotoxicity due to cisplatin and nucleoside analogues). To the extent that is possible, care should be taken to avoid medications that have an overlapping toxicity profile with cisplatin, 5-FU, and cetuximab.
- Antiviral Therapy: It is highly suggested but not required, that patients receive antiviral medications while on study. Antiviral regimens may be modified during the course of protocol treatment as necessitated by the occurrence of drug induced toxicity or based upon measurement of HIV viral load. If antiviral agents are to be initiated or changed between study enrollment and the start of study treatment, then a viral load measurement should be taken before and after the change. The choice of antiviral medications is to be left to the treating physician’s discretion as this is often a decision that requires individualization. However, it is recommended to avoid antiretrovirals that cause peripheral neuropathy (stavudine, didanosine) because of the need for cisplatin therapy, those that are particularly myelosuppressive (such as zidovudine containing medications), and those that induce chronic diarrhea.
- Pneumocystis Carinii Pneumonia (PCP) Prophylaxis: Patients should receive PCP prophylaxis if they meet established guidelines for PCP prophylaxis (eg, CD4 count < 200/ $\mu$ L).
- Acyclovir or other herpes medication is strongly suggested during the course of active treatment as reactivation of HSV within the radiation treatment area may contribute to local toxicity.
- Pain Medications: It is suggested that all patients be prescribed and instructed on the use of narcotics. In general this will include a short acting agent (such as liquid morphine) in combination with a long acting agent. Titration of these agents should be addressed regularly and clinic notes should reflect pain levels and narcotic use.
- Growth Factor Support: Myeloid and erythroid growth factor support is often required in this type of study population. Prophylactic use is encouraged but not

mandated. General guidelines are to begin GCSF on day 6 following each chemotherapy cycle and continue daily through the nadir until the ANC is above 5,000. Thereafter GCSF may be used as needed. For instance, the dose may be adjusted to keep the ANC > 1000.

- Antiemetics will be required before and after cisplatin according to NCCN ([www.nccn.org](http://www.nccn.org)) and/or local institutional guidelines.
- Anti-diarrhea medications should be used at the first sign of 5-FU induced diarrhea, and may include Loperamide, Imodium, Tincture of Opium, and/or Octreotide.
- Topical medications to the area of radiation therapy injury are to be avoided unless specifically discussed with the radiation oncologist.

## 5.7 Criteria for Treatment Discontinuation

If therapy is discontinued early, patients should remain on study whenever possible. When this is not possible, see [section 5.7](#) for Criteria for Study Discontinuation. Patients may discontinue therapy before the planned completion of the study treatment for the following reasons:

- Study medication will be interrupted or permanently discontinued for treatment related toxicity as outlined in [sections 7.1–7.3](#).
- Disease progression. Further therapy will be at the discretion of the treating physician.
- Patients study treatment must be discontinued for patients who require a break in study treatment for longer than 4 weeks.
- **For any delay in treatment > 1 week, the study chair should be informed by telephone or e-mail regarding the delay, including the following information: (1) patient number, (2) date of registration, (3) total dose of radiation therapy given, (4) number of cycles of cisplatin/5FU given, (5) total number of doses of cetuximab given, (6) component(s) of treatment delayed and reason for the delay. The purpose of this communication is to inform the study chair regarding clinically significant treatment delays, and to assist treating physicians in adhering to protocol guidelines.**
- Patients who are non-compliant with respect to keeping appointments or completing required tests for the evaluation of drug safety and efficacy may be discontinued from study treatment voluntarily or by the discretion of the Investigator.
- Patients may decline to receive further therapy, or any part of the therapy, at any time. These patients will be encouraged to remain on study for follow up.
- The Investigator has the right to discontinue any portion of the study treatment, or the entire therapy for clinical reasons that he/she believes could be deleterious to the subject, even if such reasons do not fall into the toxicity classifications and dose modifications described in [sections 7.1–7.3](#).

## 5.8 Criteria for Study Discontinuation

All patients should be followed after completion of study-specified therapy for survival and disease status (progressed, relapsed, or disease-free) for 5 years. After 5 years,

additional survival and disease status is no longer required. Patients may withdraw from the study at any time prior to 5 years.

## 6.0 STUDY EVALUATIONS

*Note: ECOG sites are to follow all study requirements and will participate in all discipline reviews and sample submissions as outlined within the protocol.*

### 6.1 Baseline/Pretreatment Evaluation

The following will be obtained within the time frames specified in [Appendix I](#):

- Obtained within 6 months of registration
  - Cervical PAP for females with a cervix.
- Obtained within 6 weeks of registration
  - HIV Plasma RNA: Viral load studies will be performed locally at the institution using an ultra sensitive assay with a limit of detection of at least 50 copies/mL. If the antiviral medications were changed after this was obtained and before registration, it should be repeated prior to registration.
  - T CELLS: CD4/CD8 counts and percentages will be included in baseline labs.
  - Electrocardiogram.
- Obtained within 4 weeks of registration
  - CXR – PA and Lateral.
  - Chest CT scan if there is any suspicion of metastatic disease by history, physical, or by CXR.
  - Abdomen and pelvic CT scan (or MRI).
  - Endorectal ultrasound is encouraged if available at the institution to obtain an accurate estimate of tumor size.
- Obtained within 2 weeks of registration
  - Complete history and physical examination, including information regarding: (1) Duration of HIV and AIDS diagnoses, (2) history of major opportunistic illnesses and prior cancer diagnoses, (3) date of initial diagnosis of anal cancer and a copy of the pathology report must be available, (4) prior history of anal dysplasia and prior treatment of any such dysplasia, if known, (5) Presence of any symptoms related to the anal cancer including a quantification of pain, (6) current medications and history of drug allergies. All antiviral medications taken within the past 28 days will be documented. Current pain medication usage will be quantified.
  - Complete physical examination, including: (1) Karnofsky performance status, (2) vital signs, weight, height, (3) anal examination must include a digital rectal exam to document the size and location of the tumor pre-treatment unless this cannot be tolerated due to pain. This may be supplemented by the surgeon's exam during an exam under anesthesia performed at the time of diagnostic biopsy (which may be done more than 2 weeks prior to registration, (4) assessment of inguinal lymph

nodes. Palpable or otherwise abnormal inguinal lymph nodes (such as those that appear abnormal on radiographic imaging) should be subjected to fine needle biopsy whenever possible.

- Routine Laboratory Testing: Baseline laboratory testing will include CBC (including WBC, differential, hemoglobin, hematocrit, platelet count), and CHEMISTRY PANEL (including creatinine, total and direct bilirubin, AST(SGOT), ALT(SGPT), alkaline phosphatase, albumin and serum electrolytes (sodium, potassium, chloride, bicarbonate) and serum magnesium.
- Pregnancy Test: Pregnancy test (urine  $\beta$ -HCG) will be performed (and results obtained) within 14 days of treatment initiation when indicated (sexually active females of child bearing potential).

➤ After consent but before treatment is initiated

- The EORTC quality of life instruments, QLQ-C30 and QLQ-CR38, and the Memorial Sloan-Kettering Cancer Center anal function criteria (MSK-AF) (See [Appendix V](#)). This information will be collected and entered in AdvantageEDC via the QLC form. The QLQ form will be used to submit all Quality of Life data not faxed to the AMC Operations & Data Management Center as of August 22, 2008. All previously submitted Quality of Life data will be captured in AdvantageEDC by the AMC Operations & Data Management Center.
- Anal swab for HPV testing and cytology (see [Appendix VI](#)).
- Optional tumor biopsy for research purposes ([Appendix IX](#)).
- Optional resolution anoscopy: In sites that have the capacity to perform high resolution anoscopy, this exam will be performed at baseline and at month 6. The clinical exam will be described and a clinical assessment will be made as to the presence of dysplasia. At month 6, biopsies will not be required but may be performed if warranted by a high suspicion for cancer, as biopsies obtained from a previously irradiated field may lead to non-healing ulcers. Any decision to perform a subsequent Pap or high resolution anoscopy (HRA) over the next 4.5 years while patients remain on study will be made on clinical grounds and not for study purposes.

➤ After consent and registration, but within 28 days after registration

Submission of the tissue block from the original biopsy (see [Appendix VI](#)) and frozen tissue from the optional biopsy (if performed) (see [Appendix IX](#)).

### Tissue Samples

Histologic confirmation of the anal cancer diagnosis is required for enrollment. Central Pathology Review of the primary tumor will be performed. A tissue block along with a copy of the surgical pathology report must be submitted ([Appendix VI](#)). If the block is not available, a representative H & E stained section and ten unstained slides should be submitted. All materials will be retained unless return is specifically requested. If an FNA with cytology was obtained for diagnostic purposes instead of a biopsy, this will suffice if a cell block was prepared.



Although it is optional, fresh frozen tissue obtained before the start of therapy is requested whenever possible for research purposes. This should be sent to the ACSR tissue bank for storage ([Appendix IX](#)) and REQUIRES a separate consent form. The tissue can be obtained at the time of the exam under anesthesia if a patient has signed an ACSR donation consent form or at the time of endoscopic ultrasound (US) of the rectum, again if this ACSR donation consent has been signed. As an alternative to obtaining a biopsy, a FNA sample could also be obtained for this purpose. The ideal location is from the primary tumor; however, if a biopsy or FNA is planned of a metastatic site such as the inguinal nodes, then collecting the research material can be done at the same time from that site.

It is expected that tissue may be evaluated for HPV detection and typing, gene expression by microarray analysis and potentially other research assays as additional correlative science studies are developed. These evaluations will not be done in real time.

➤ **Quality of Life Survey**

The EORTC quality of life instruments, QLQ-C30 and QLQ-CR38, and the Memorial Sloan-Kettering Cancer Center anal function criteria (MSK-AF) will be completed (via the QLQ form in Advantage EDC) at baseline, at treatment completion, at week 12 (i.e., month 3), then at week 26 and months 12, 24 and 36. The QLQ form will be used to submit all Quality of Life data not faxed to the AMC Operations & Data Management Center as of August 22, 2008. All previously submitted Quality of Life data will be captured in AdvantageEDC by the AMC.

➤ **Patient Care in Preparation of Treatment**

A vascular access device, a home infusion company and home nursing agency may be needed to coordinate the 5-FU infusion, unless the patient is to be admitted for this therapy.

## **6.2 Evaluations During and Immediately after Treatment**

### **6.2.1 Week 1 (Day 1)**

- Initial chemotherapy and radiation therapy is to begin on this day.
- At baseline, a focused H & P will include:
  - History and physical exam.
  - PREGNANCY TEST: Pregnancy test (urine  $\beta$ -HCG) will be performed whenever it is felt to be warranted by clinical judgment while on active therapy.

### **6.2.2 Week 2 (Day 8 +/- 3 days)**

- A focused H & P is required weekly during active therapy and additionally as needed. Include:
  - Concurrent medications, vital signs, KPS, weight. Changes in underlying HIV disease such as intercurrent illness or other changes in health status.

- Symptoms recorded. Quantify usage of pain medication and growth factors.
- Toxicity documentation will include an anogenital inspection to document the local toxicity of radiation therapy.
- Requirement for myeloid or erythroid growth factors, or transfusions will be documented.
- Focused physical exam as indicated. Digital rectal exam may not likely be possible due to tumor symptoms or the presence of toxicity, but whenever possible, the tumor size should be documented on a weekly basis.
- Laboratory Testing
  - CBC weekly (and additionally as needed) through the end of the active therapy. Abnormal results should be repeated in 3-4 days time (2 per week) when the ANC is < 1000 or Platelet count is < 50K.
  - CHEMISTRY PANEL and serum Mg<sup>++</sup> should be performed at week 2, 3, 4, 5, 6, 7, 8, and 9, and as needed.
- Submission of radiation therapy port films, boost films, and treatment
  - Please refer to the QARC Submission Schedule for radiation materials found on page 39 for an itemized list of submission materials and instructions regarding the timing of submissions.
  - All submission materials should be sent to the address noted in [section 5.5.9.4](#).

#### 6.2.3 Week 3 (Day 15 +/- 3 days)

- Focused H & P as above in [section 6.2.2](#) (week 2)
- Laboratory Testing
  - CBC, platelet count, differential (repeated in 3-4 days PRN as noted in 6.2.2)
  - CHEMISTRY PANEL

#### 6.2.4 Week 4 (Day 22 +/- 3 days)

- Focused H & P as above in [section 6.2.2](#) (week 2)
- Laboratory Testing
  - CBC and CHEMISTRY PANEL.
  - Electrolytes, BUN, Creatinine, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, AST, ALT, Albumin.
- Treatment Planning
  - Most patients will receive cycle 2 of their chemotherapy beginning on Day 29 and arrangements should begin the week prior.

#### 6.2.5 Week 5 (Day 29 +/- 3 days)

- Day 29 chemotherapy initiated.
- Complete H & P (see [section 6.1](#))

- Laboratory Testing
  - CBC and CHEMISTRY PANEL.
  - HIV viral load: Viral load study on Days 29 and 57 (will be performed locally at the institution).
  - T CELLS: CD4/CD8 counts and percentages on Days 29 and 57.
  - Quality of Life Instruments (EORTC QLQ-C30 and QLQ-CR38 and MSK-AF) via the QLQ form in AdvantageEDC. The QLQ form will be used to submit all Quality of Life data not faxed to the AMC Operations & Data Management Center as of August 22, 2008. All previously submitted Quality of Life data will be captured in AdvantageEDC by the AMC.

#### 6.2.6 Week 6 (Day 36 +/- 3 days)

- Focused H & P as above in 6.2.2 (week 2).
- Laboratory testing:
  - CBC and CHEMISTRY PANEL.

#### 6.2.7 Week 7 (Day 43 +/- 3 days)

- Focused H & P as above in 6.2.2 (week 2).
- Laboratory testing:
  - CBC and CHEMISTRY PANEL.

#### 6.2.8 Week 8 (Day 50 +/- 3 days)

- Focused H & P as above in 6.2.2 (week 2).
- Laboratory testing:
  - CBC and CHEMISTRY PANEL.

#### 6.2.9 Week 9 (Day 57 +/- 5 days)

- Complete H & P (see [sections 6.1](#)).
- Laboratory testing:
  - CBC and CHEMISTRY PANEL.
  - HIV viral load will be performed locally at the institution.
  - T CELLS: CD4/CD8 counts and percentages.

#### 6.2.10 Additional Weeks

If therapy has been delayed, the same requirements of weekly focused examinations and laboratory studies will continue until at least 2 weeks after the completion of therapy. If residual grade 3 or greater toxicity persists, patients should be evaluated every 2 weeks with appropriate studies until the toxicity has dropped to grade 2 or lower.

## 6.3 Evaluations after Completion of Therapy

### 6.3.1 Week 12 (Day 78 +/- 14 days)

- Complete H & P
- Laboratory Testing
  - CBC and CHEMISTRY PANEL.

Quality of Life Instruments (EORTC QLQ-C30 and QLQ-CR38 and MSK-AF) via the QLQ form in AdvantageEDC. The QLQ form will be used to submit all Quality of Life data not faxed to the AMC Operations & Data Management Center as of August 22, 2008. All previously submitted Quality of Life data will be captured in AdvantageEDC by the AMC.

- Radiographic Studies

CXR and abdominal and pelvic CT scan.

These studies will be performed once therapy is complete and acute inflammation has resolved. This may be delayed if therapy was late finishing due to lengthy treatment breaks for example, as scans will be difficult to perform and interpret if significant pelvic inflammation is still present. Alternatively, these may be performed early if residual or recurrent disease is suspected and results are required on clinical grounds.

- Biopsy

Whenever residual or progressive disease is suspected, radiographic imaging or biopsy may be performed as indicated. One caveat is that a full thickness biopsy within the radiation field can be complicated by the development of a non-healing ulcer. An FNA could be used as an alternative to a full thickness biopsy. Because a potentially curative procedure such as an APR for uncontrolled local disease may be warranted, concern about the risk of a biopsy should not delay an appropriate evaluation for residual disease.

- Submission of Radiation Therapy Boost Films and Treatment Record

Please refer to the QARC Submission Schedule for Radiation Material found on page 39 for an itemized list of submission materials and instructions regarding the timing of submissions.

All submission materials should be sent to the address noted in [section 5.5.9.4](#).

### 6.3.2 Week 18 (+/- 14 days)

- Focused H & P including but not limited to:
  - Concurrent medications and vital signs, weight, KPS
  - Pain medication usage quantified

- Residual toxicity such as neuropathy, need for myeloid or erythroid growth factor support
- Assess for tumor relapse, changes in underlying HIV disease such as intercurrent illness or other changes in health status (evaluation by PE is acceptable)
- Radiographic and laboratory studies as indicated

#### 6.3.3 Week 26 (+/- 14 days)

- Complete H & P including but not limited to:
  - Concurrent medications and vital signs, weight, KPS
  - Pain medication usage quantified
  - Assess for tumor relapse (including an exam of the anus and inguinal lymph nodes), residual toxicity, changes in underlying HIV disease such as intercurrent illness or other changes in health status
  - Laboratory testing:
    - CBC and CHEMISTRY PANEL
    - HIV viral load will be performed locally
    - CD4/CD8 counts and percentages
    - Radiographic Studies if indicated by H & P
  - Quality of Life Instruments (EORTC QLQ-C30 and QLQ-CR38 and MSK-AF) Via the QLQ form in AdvantageEDC. The QLQ form will be used to submit all Quality of Life data not faxed to the AMC Operations & Data Management Center as of August 22, 2008. All previously submitted Quality of Life data will be captured in AdvantageEDC by the AMC
  - Repeat anal swab for HPV, anal cytology ([Appendix VI](#))
  - High resolution anoscopy (if available): In sites that have the capacity to perform high resolution anoscopy, this exam will be performed at baseline and at month 6. The clinical exam will be described and a clinical assessment will be made as to the presence of dysplasia. At month 6, biopsies will not be required but may be performed if warranted by a high suspicion for cancer, as biopsies obtained from a previously irradiated field may lead to non-healing ulcers. Any decision to perform a subsequent Pap or high resolution (HR) anoscopy over the next 4.5 years while patients remain on study will be made on clinical grounds and not for study purposes.

#### 6.3.4 Month 9 (+/- 14 days)

- Complete H & P as above (see week 26)
- Laboratory testing:
  - CBC and CHEMISTRY panel
  - Radiographic Studies if indicated by H & P

#### 6.3.5 Month 12 (+/- 14 days)

- Complete H & P as above (see week 26).
- Laboratory testing:

- CBC and CHEMISTRY panel.
- HIV viral load will be performed locally, CD4/CD8 counts and percentages
- Radiographic Studies if indicated by H & P.
- Quality of Life Instruments (EORTC QLQ-C30 and QLQ-CR38 and MSK-AF) via the QLQ form in AdvantageEDC. The QLQ form will be used to submit all Quality of Life data not faxed to the AMC Operations & Data Management Center as of August 22, 2008. All previously submitted Quality of Life data will be captured in AdvantageEDC by the AMC.

#### 6.3.6 Months 18, 24 and 30 (+/- 1 month)

- Complete H & P as above (see week 26)
- Laboratory testing:
  - CBC and CHEMISTRY panel.
  - Quality of Life Instruments (EORTC QLQ-C30 and QLQ-CR38 and MSK-AF) via the QLQ form in AdvantageEDC for month 24 follow-up only.
  - Radiographic Studies if indicated by H & P.

#### 6.3.7 Month 36 (3 Years +/- 1 month)

- Complete H & P including an exam of the anus and inguinal lymph nodes.
- Laboratory testing:
  - CBC and CHEMISTRY panel.
  - Additional laboratory testing will be performed as indicated.
  - HIV viral load will be performed locally, CD4/CD8 counts and percentages.
  - Radiographic Studies if indicated by H & P.
  - Quality of Life Instruments (EORTC QLQ-C30 and QLQ-CR38 and MSK-AF) via the QLQ form in AdvantageEDC

#### 6.3.8 Month 48 (4 Years +/- 1 month)

- Same as in 6.3.6 above.

#### 6.3.9 Month 60 (5 Years +/- 1 month)

- Complete H & P including an assessment of tumor status.
- Laboratory testing:
  - CBC and CHEMISTRY panel.
  - Additional laboratory testing will be performed as indicated.
  - HIV viral load will be performed locally, CD4/CD8 counts and percentages.
  - Patients are taken off study at this time point.

#### 6.4 Off Study Evaluation

For patients that withdraw from the study prematurely, the following evaluations will be performed whenever possible, preferably at the time of or up to 1 month after withdrawal from the study:

1. History and physical: A full history and physical exam.
2. Anogenital exam: A digital rectal exam to document local control. If there is an abnormality that suggests tumor, an FNA or biopsy should be performed. Tumor size should be documented. The anogenital region will also be evaluated for toxicity.
3. Anal swab for HPV testing ([Appendix VI](#)).
4. Routine laboratory testing: CBC and CHEMISTRY panel.
  - HIV viral load will be performed locally.
5. HIV viral load
6. T Cells: CD4/CD8 counts and percentages.
7. Quality of life survey: The final quality of life assessment will be performed unless the subject is more than 36 months into the study and has completed the 36 M QOL surveys. This will be completed via the QLQ form in AdvantageEDC.

## 7.0 DOSE MODIFICATION/TOXICITY MANAGEMENT

This study will utilize the NCI's Common Terminology Criteria for Adverse Events and the RTOG/EORTC Late Morbidity Scoring Scheme ([Appendix IV](#)). A copy of the CTCAE can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>).

Dose adjustments may be necessary due to toxicity. **The decision regarding treatment adjustment or discontinuation from drug therapy or radiation therapy for suspected treatment associated toxicity must follow the protocol guidelines but ultimately rests with the investigator.** The investigator must use the available data and exercise clinical judgment.

Attribution of toxicity to one therapy may be difficult when there are three concurrent agents with overlapping toxicities being given as components of the CMT. Dose modifications or dose delays may be due to multiple causes. **Judgment is needed in deciding if more than one agent is to be held or modified.**

**If radiation therapy is being held because of local toxicity, chemotherapy and cetuximab will also be held until the radiation therapy is resumed.** It is possible that radiation therapy will be permanently discontinued yet the treating physician may still wish to give a second cycle of chemotherapy. That will be permitted if the following criteria have been met.

**If there are conflicting rules regarding dose reduction (i.e., a 25% dose reduction is specified based on the nadir blood counts following cycle 1, but a 50% dose reduction is specified due to delayed and/or incomplete count recovery) then the greater reduction, i.e. the more conservative guideline, will be followed.**

**Concurrent illness such as a severe opportunistic infection may interrupt therapy. A break of greater than 8 weeks should result in treatment discontinuation. If therapy is to be resumed, this decision should be discussed first with one of the study chairs.**

### 7.1 Hematologic Toxicity

#### 7.1.1 Dose Delay of Cycle 2 of chemotherapy (and cetuximab)

Cycle 2 chemotherapy (and continued weekly cetuximab) will be delayed if there has been a break required in radiation therapy. The goal is to continue to provide concurrent cetuximab plus chemo- and radiotherapy. See [section 5.0](#) for details.

Cycle 2 chemotherapy should not be resumed until there has been adequate recovery from any hematologic toxicity induced by cycle 1. The ANC should be  $\geq 1200$  and platelet count  $\geq 100,000$ . In this case, concurrent cetuximab may continue if radiation therapy is continuing. In order to continue to provide concurrent therapy, cycle 2 of chemotherapy should be given before the last week of radiation therapy begins. See [section 7.2.3](#) regarding radiation therapy breaks for hematologic toxicity. If after one week of delay, the ANC is  $> 1200$  and



platelets are > 100,000 full dose therapy will be administered. If the ANC has not returned to > 1,200 or platelets are not > 100,000 after the one week delay, the drug doses will be modified as follows:

ABSOLUTE NEUTROPHIL COUNT			
COUNT	$\geq 1,200 / \text{mm}^3$	750 - 1,199/ $\text{mm}^3$	$< 750 / \text{mm}^3$
$\geq 100 \text{ K}$	Full Dose	50% 5-FU, 50% Cisplatin	Hold Cisplatin/5-FU
75-99 K	50% 5-FU, 50% Cisplatin	50% 5-FU, 50% Cisplatin	Hold Cisplatin/5-FU
$< 75 \text{ K}$	Hold Cisplatin/5-FU	Hold Cisplatin/5-FU	Hold Cisplatin/5-FU

If by these guidelines, treatment is to be held, then radiation therapy may need to be held in addition. A treatment hold becomes a treatment discontinuation as defined in [section 5.7](#).

When there is a conflict in these instructions, it is advised that the issue be discussed with one of the study chairs.

#### 7.1.2 Dose Modification of Cycle 2 Chemotherapy Based on Nadir

Dose Modification for Cycle 2 Chemotherapy based on Hematologic Nadir with Cycle 1:

ABSOLUTE NEUTROPHIL COUNT NADIR			
PLATELET NAIDR**	$\geq 500 / \text{mm}^3$	$< 500 / \text{mm}^3$ for $< 4$ days	$< 500 / \text{mm}^3$ confirmed for $\geq 4$ days
$\geq 40 \text{ K}$	Full Dose	75% 5-FU, 75% Cisplatin	50% 5-FU, 50% Cisplatin
20-39 K	75% 5-FU 75% Cisplatin	75% 5-FU, 75% Cisplatin	50% 5-FU, 50% Cisplatin
$< 20 \text{ K}$	50% 5-FU 50% Cisplatin	50% 5-FU, 50% Cisplatin	25-50% 5-FU, 25-50% Cisplatin

Notes:

75% 5-FU or 75% CDDP = chemotherapy dose to be delivered, representing a 25% dose reduction

***The 50-75% dose reduction for severe neutropenia and thrombocytopenia covers a range to allow for discretion of the treating physician.***

## 7.2 Non-Hematologic Chemotherapy-Associated, Radiation-Associated, and Cetuximab-Associated Toxicity

### 7.2.1 5-FU Dose Modification

Severe GI Toxicity is likely the result of extreme sensitivity to 5-FU. Before initiation of 5-FU, patients will be instructed to begin therapy such as Lomotil and

oral hydration if they should develop diarrhea. If the diarrhea is unresponsive to Lomotil, if 8 or more Lomotil tablets per 24 hours are required to control the diarrhea, or if cramping, abdominal pain or bleeding are present, the patient should report this immediately to his physician. Appropriate therapy (such as Tincture of Opium or Octreotide, hydration, pain control, electrolyte replacement) and evaluation (examination, laboratory monitoring of electrolytes) should be initiated as clinically appropriate.

**The development of grade 3-4, 5-FU induced diarrhea before the end of the 96-hour infusion, should lead to immediate discontinuation of the infusion.**

**Dose Modifications for Cycle 2 Chemotherapy Based on Diarrhea or Stomatitis**

Toxicity	Parameters	Agent	Modification for Cycle 2
Diarrhea	Grade 3 Increase of $\geq 7$ stools/day or incontinence; or need for parenteral support for dehydration	5-FU	75% 5-FU
Diarrhea	Grade 4 Physiologic consequences requiring intensive care; or hemodynamic collapse	5-FU	50% 5-FU
Stomatitis	Grade 3 Painful erythema, edema, or ulcers requiring IV hydration	5-FU	75% 5-FU
Stomatitis	Grade 4 Severe ulceration or requires parenteral nutritional support	5-FU	50% 5-FU

### 7.2.2 CDDP Dose Modification

➤ Renal Insufficiency, NeuroToxicity, Ototoxicity:

A serum creatinine of 1.5-2.0 X ULN on Day 29 (or the planned day of cycle 2 cisplatin dose) will result in a 50% reduction in the dose of cisplatin for cycle 2. The second dose of cisplatin will be withheld if the serum creatinine is greater than 2.0 X ULN on Day 29 (or the planned day of cycle 2 cisplatin). At the discretion of the investigator mitomycin (at a dose of 10 mg/m<sup>2</sup> or 20 mg maximum) may be substituted in cycle 2 for toxicity that is felt to be CDDP dependent and specific.

If the serum creatinine rose significantly following cycle 1 but has recovered to < 1.5 X ULN when cycle 2 is due, then several options are suggested. Either a 25% dose reduction or improved post CDDP hydration (such as daily IV hydration for several days) or both are potential interventions.

Tinnitus, hearing loss, or grade 3 peripheral neuropathy will result in a 50% reduction in the dose of cisplatin. Grade 4 neuropathy will result in no further CDDP being given. Investigator discretion will allow the use of mitomycin (at a dose of 10 mg/m<sup>2</sup> or 20 mg maximum) to be substituted for cycle 2 if the

toxicity is felt to be CDDP dependent. The table also describes dose modifications for CDDP induced ototoxicity.

**Dose Modifications for Cycle 2 Chemotherapy Based on Cycle 1 Toxicity**

<b>Toxicity</b>	<b>Parameters</b>	<b>Agent</b>	<b>Modification</b>
Creatinine	1.5 - 2.0 X ULN	CDDP	50% CDDP
Creatinine	> 2.0 X ULN	CDDP	Hold Consider mitomycin
Ototoxicity ( <i>Inner ear/hearing</i> )	Grade 2 Tinnitus or hearing loss, not requiring hearing aid or treatment.	CDDP	50% CDDP
Ototoxicity ( <i>Inner ear/hearing</i> )	Grade 3 Tinnitus or hearing loss, correctable with an aid or treatment.	CDDP	50% CDDP Consider mitomycin
Neuro: ( <i>Sensory, Motor</i> )	Grade 2 Motor or Grade 3 Sensory loss or paresthesia interfering with activities of daily living.	CDDP	50% CDDP Consider mitomycin
Neuro: ( <i>Sensory, Motor</i> )	Grade 3 Motor or any Grade 4 Peripheral neuropathy	CDDP	Hold CDDP Consider mitomycin

### 7.2.3 Radiation Therapy Modification for Non-hematologic Toxicity

Contact the radiation oncology protocol co-chair (Lisa S. Kachnic, MD, see page 5 for contact information) by telephone or email for the indications outlined below. Please include the following information in your communication: (1) patient ID number, (2) treating physician name, (3) date of question, (4) date radiation therapy started, (5) number of radiation doses given to date, (6) cumulate radiation dose given to date, (7) question/problem. The radiation oncology co-chair will document any deviations in the protocol:

- The treating physician wishes to interrupt radiation during the first 28 days of the treatment program. Permission must be obtained from the radiation oncology co-chair.
- If RT is suspended for > 10 days, contact the study chair all study chair before proceeding.
- Any deviation from the radiation therapy program not specified in the protocol.

Radiation therapy may be held interrupted for the following indications:

- ANC < 500/mm<sup>3</sup> and/or platelets < 40,000: RT will resume when ANC > 500 and PLT > 40,000. If chemotherapy is being held in order to allow for count recovery, radiation therapy can be held as well, based on treating physician discretion. If radiation is held due to cytopenia, laboratory monitoring should increase to include twice per week CBC, differential, and platelet count until recovery to an ANC.

- Grade 3 or greater diarrhea (> 6 stools/day above baseline): resume when RT is < 6 stools/day above baseline.
- Grade 4 vomiting (parenteral nutrition, intensive care, or hemodynamic collapse): resume when vomiting is < grade 3.
- Grade 4 skin ulceration: resume when the skin reaction is grade 2 or less. If localized or generalized infection develops secondary to an area of confluent moist desquamation, radiation therapy will be suspended. In this setting, radiation therapy will be resumed after there has been complete resolution of sepsis and re-epithelialization in the area of desquamation. The presence of moist desquamation in the absence of infection shall not constitute grounds for unplanned suspension of radiation therapy.

#### 7.2.4 Cetuximab-Associated Toxicity and Dose Modifications

Cetuximab should be held if radiation therapy is held for toxicity, or if both chemotherapy and radiation therapy are held for toxicity. A minimum of 6 and maximum of 8 doses of cetuximab should be administered.

##### 7.2.4.1 Infusion Reactions

Severe infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistamine pre-medications (e.g., diphenhydramine) in subsequent doses. If the patient experiences a mild or moderate (grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%. For grade 1 or 2 reactions manifesting only as delayed drug fever, see below in [section 7.2.4.2](#).

Cetuximab should be immediately and permanently discontinued in patients who experience severe (grade 3 or 4) infusion reactions.

##### 7.2.4.2 Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated

drug fever following premedication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.

#### 7.2.4.3 Pulmonary Toxicity

In the event of acute onset (grade  $\geq 2$ ) or worsening pulmonary symptoms which are not thought to be related to underlying cancer, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. Cetuximab retreatment should not occur until these symptoms have resolved to grade 1. If interstitial lung disease is confirmed, cetuximab should be discontinued and the patient should be treated appropriately.

#### 7.2.4.4 Dermatologic Toxicity

Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe acneform rash. Treatment with topical and/or oral tetracyclines should be considered; topical corticosteroids are not recommended.

Dry skin will be noted in most patients receiving cetuximab. This should be treated with an emollient twice daily.

With prolonged use of cetuximab, some patients may develop paronychia inflammation of the fingers and toes or fissuring of the fingertips. In general, good hygiene with appropriate local measures such as soaks in aluminum acetate (Burow's) solution BID-QID will prevent secondary infection. Symptom relief may be achieved with standard bandages or with the application of liquid bandages (cyanoacrylate preparations such as Band-Aid Liquid Bandage®).

If a patient experiences severe acneform rash, cetuximab treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification.

Cetuximab Dose Modification Guidelines			
Grade 3 Acneiform Rash	Cetuximab	Outcome	Cetuximab Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m <sup>2</sup>
		No Improvement	Discontinue cetuximab
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m <sup>2</sup>
		No Improvement	Discontinue cetuximab
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m <sup>2</sup>
		No Improvement	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

Dose levels for cetuximab are as follows:

Cetuximab Dose Levels	
	Weekly Cetuximab Dose
Starting dose	250 mg/m <sup>2</sup>
Dose Level –1	200 mg/m <sup>2</sup>
Dose Level –2	150 mg/m <sup>2</sup>

#### 7.2.4.5 Cardiac Toxicity

Cardiac ischemia/infarction and acute cardiomyopathy are known side effects of infusional 5-FU based chemotherapy. There have been several reports of such events in patients receiving cetuximab with infusional 5-FU regimens. The following guidelines apply for patients who develop cardiac toxicity:

- Grade 4 cardiac event: Discontinue cetuximab permanently. The decision to resume chemotherapy should be carefully made based on the physician's discretion and discussion with the patient. If retreatment with chemotherapy is considered, it should be delayed for a minimum of 2-3 weeks from the last dose of cetuximab AND after full recovery from the cardiac event. In addition, the dose of chemotherapy should be reduced by one dose level. Patients should be monitored carefully, as cardiac events may recur upon rechallenge.
- Grade 3 cardiac event: The treating physician may discontinue cetuximab, or contact the study chair to discuss the event and determine if rechallenge with cetuximab is appropriate.

#### 7.2.4.6 Management of Hypomagnesemia

Hypomagnesemia has been reported with cetuximab when administered as a single agent and in combination with multiple different

chemotherapeutic regimens. The incidence of hypomagnesemia (both overall and severe [NCI TC grades 3 and 4]) is increased in patients receiving chemotherapy and cetuximab as compared with those receiving chemotherapy alone based on controlled clinical trials. Patients receiving cetuximab therapy should be monitored for hypomagnesemia. Magnesium repletion may be necessary based on clinical judgment.

## 8.0 ADVERSE EVENTS

This study will utilize the NCI's Common Terminology Criteria for Adverse Events and the RTOG/EORTC Late Morbidity Scoring Scheme ([Appendix IV](#)). CTCAE version 3.0 will be utilized for AE reporting until June 30, 2011. CTCAE version 4.0 will be utilized beginning July 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0 and 4.0. A copy of the CTCAE version 3.0 and 4.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov/reporting/ctc.html>). The document "CTEP, NCI Guidelines: Adverse Event Reporting Requirements for NCI Investigational Agents" (sections 2 and 3) clearly outlines reporting criteria.

### 8.1 Classification of Adverse Events by Severity and Relationship to Study Drug

- Adverse Event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).
- Life-threatening Adverse Event: Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Serious Adverse Event (SAE): Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Please note for hospitalization: All hospitalizations (or prolongation of existing hospitalization) for medical events equivalent to CTCAE grade 3, 4, 5 must be reported regardless of the requirements for Phase of study, expected or unexpected, and attribution. For example, do not report an admission for pharmacokinetic sampling, but do report an admission for a myocardial infarction. For this study, hospitalization for expedited AE reporting purposes is defined as an inpatient hospital stay equal to or greater than 24 hours. A hospital visit where a patient is admitted for observation or minor treatment (e.g., hydration) and released in less than 24 hours would not meet the requirements for hospitalization.
- Toxicity: Toxicity is a term NOT clearly defined by regulatory organizations. Toxicity has been described as an AE that has an attribution of possibly, probably or definitely related to investigational treatment. To minimize confusion the NCI would recommend that the term toxicity NOT be utilized for AE reporting purposes.



- Unexpected Adverse Event: Any AE that is not listed in the NCI Agent Specific Expected Adverse Event List. This list is updated electronically in real time.
- Attribution: The determination of whether an AE is related to a medical treatment or procedure. Attribution categories:
  - Definite – The AE is *clearly related* to the investigational agent(s).
  - Probable – The AE is *likely related* to the investigational agent(s).
  - Possible – The AE *may be related* to the investigational agent(s).
  - Unlikely – The AE is *doubtfully related* to the investigational agent(s).
  - Unrelated – The AE is *clearly NOT related* to the investigational agent(s).

## 8.2 Reporting of AEs

Commercial agents (Cisplatin, 5-FU) are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. The NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and, unless specified otherwise in the protocol, the following procedures should be followed.

Refer to the pharmaceutical section of the protocol document to determine if an agent is investigational or commercial. Also see sections 2.10 and 2.11 of the “NCI Guidelines: Expedited Adverse Event Reporting Requirements” for definitions.

All AEs, regardless of severity, and whether or not ascribed to the study drug administration, will be recorded in the appropriate section of the CRF. Patients withdrawn from the study due to AEs will be followed by the Investigator until the outcome is determined and, when appropriate, additional written reports and documentation will be provided.

## 8.3 Expedited AE Reporting

Expedited AE reporting for this study will occur via the CTEP Adverse Event Reporting System (CTEP-AERS) accessed via the CTEP home page. (<http://ctep.cancer.gov>). Expedited reporting requirements are outlined in the table in [section 8.3.1](#). CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Protocol Study Chair, Principal Investigator at the local AMC treating institution, and AMC Operations Center. CTEP-AERS provides a copy feature for other e-mail recipients. All reported SAEs will be reviewed by the Protocol Study Chair to determine if further action is necessary.

A 24-hour notification is to be made to the AMC ODMC by telephone at 301-251-1161, only when Internet connectivity is disrupted. Once Internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

### 8.3.1 Expedited Reporting Requirements for AEs that occur within 30 Days of Last Protocol Treatment

	1	2	2	3		3		4 & 5	4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected With Hospitalization	Without Hospitalization	Expected With Hospitalization	Without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

<sup>1</sup>Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment require reporting as follows:

- 24-hour notification followed by complete report within 5 calendar days for:
  - Grade 4 and Grade 5 unexpected events
- Complete SAE report within 10 calendar days:
  - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
  - Grade 5 expected events

<sup>2</sup>Although 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Cardiac: Any grade 3-5 cardiac event must be reported via CTEP-AERS regardless of the attribution and designation as expected or unexpected.

*Note: If the event is a grade 4-5 unexpected event with an attribution of possible, probable, or definite, the investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report. Otherwise, the investigator must report the AE via CTEP-AERS within 10 calendar days.*

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- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via CTEP-AERS according to the procedures outlined in [section 8.3.1](#) within 24 hours of learning of the event followed by a complete AE report submitted via CTEP-AERS within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” – A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited AE reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS according to the guidelines as described above.
- All type III AEs as defined in [section 8.4](#) must be reported within 5 calendar days via the “Type III Adverse Event Reporting Form”. All Type I and II AEs meet the criteria for CTEP-AERS reporting.

#### **8.4 Safety and Treatment Monitoring**

The following AEs will be classified as type I, II, or III for the purposes of safety analysis: (a) Type I AEs -- any grade 5 event possibly, probably, or definitely attributed to treatment, or grade 4 cardiac toxicity, (b) Type II AE - grade 4 radiation associated skin or diarrhea, (c) Type III AE - (1) any interruption in radiation therapy lasting more than 7 days, (2) failure to complete at least 6 courses of cetuximab and 2 cycles of cisplatin and 5-FU due to toxicity, and (3) failure to complete the prescribed course of irradiation due to toxicity. Patients who develop type I, II, and III events concurrently should be reported at the same time. Patients who develop type I, II, and III events at different times should have each episode reported separately. Type I and II AEs are captured by the AMC AE Form and must also be reported via CTEP-AERS. Type III AEs will be captured by the “Type III Adverse Event Reporting Form” developed for this protocol.

#### **8.5 Reporting Secondary Malignancies**

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

#### **8.6 Adverse Event Reporting for ECOG Investigators**

All ECOG Investigators are responsible for reporting adverse events according to the NCI guidelines. ECOG investigators should assess adverse events according to the instructions and tables in [Section 8.0](#) of the protocol. All reporting should be conducted within the time frames specified in [Section 8.0](#) of the protocol. Both 24 hour and written/electronic adverse event reports should be made directly to the AMC and other appropriate regulatory agencies according to the instructions in that section.

Adverse events determined to be reportable must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials

following their chemotherapy for cancer must be reported to the AMC and ECOG in accordance with [Section 8.5](#).

## **9.0 END POINT DEFINITIONS AND RESPONSE CRITERIA**

### **9.1 Toxicity Criteria and Definitions**

All eligible patients receiving at least one dose (i.e., 1 day) of therapy will be evaluable for toxicity and efficacy. All toxicity will be graded and summarized by severity grade. All toxicity will be monitored, categorized and graded by severity using the NCI's Common Terminology Criteria for Adverse Events. A copy of the CTCAE can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). The RTOG late Toxicity Criteria are included in [Appendix IV](#).

If a colostomy is required, a designation of the reason (i.e., for control of disease, management of toxicity or both) will be obtained.

Toxicity will be categorized as acute or late. Acute toxicity is defined as that seen during CMT and during the 90 days following the last dose of therapy. Late complications are classified according to the RTOG grading system ([Appendix IV](#)).

Toxicity will be categorized as local or systemic. Local toxicity will likely be limited to radiation induced skin and mucosal injury in the radiation field and can be acute or chronic.

The requirement for, duration of, and reason for hospitalization and or treatment breaks will also be recorded.

The median and range of baseline CD4 count and HIV viral load will be reported. These values will be compared to similar values at week 12, month 6 and month 12.

The proportion of patients progressing to AIDS will be reported.

### **9.2 Response Criteria**

Responses will be determined by use of the new NIH guidelines for tumor response: Response Evaluation Criteria in Solid Tumors (RECIST Criteria).

All patients will be evaluated for clinical response or progression by physical examinations, by imaging studies at baseline and at the conclusion of therapy following resolution of serious toxicity, and when appropriate, histology.

#### **9.2.1 Measurability of Tumor Lesions at Baseline**

At baseline, tumor lesions will be categorized as follows: measurable or non-measurable. The term "evaluable" is not recommended. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

At baseline, tumor lesions will be categorized as follows:

- *Measurable*: Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as 20 mm with conventional techniques or as 10 mm with spiral CT scan or MRI. Clinically detected lesions will be considered measurable when they are superficial (e.g., skin or mucosal nodules and palpable lymph nodes). Documentation by a ruler or calipers to estimate the size of the lesion is recommended.
- *Nonmeasurable*: All other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan or MRI) and truly nonmeasurable lesions.

Patients that have had an excisional biopsy of their anal cancer at the time of diagnosis may have no measurable disease. Because response rate is a secondary endpoint, patients with no measurable disease are eligible for study entry if they met the other eligibility criteria.

- *Chest x-ray*: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable and will be required when the chest x-ray is abnormal at baseline.
- *CT and MRI*: Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm.
- *Ultrasound*: Endoscopic ultrasound, supplemented by clinical examination may be useful in selected cases for assessment of tumor in the anal canal either at baseline or to confirm the complete disappearance of these lesions. This is not required but it is suggested.
- *Cytology and histology*: Histologic confirmation of disease is required prior to enrollment is required.

#### 9.2.2 Response Evaluation Criteria in Solid Tumors (RECIST Criteria)

##### ➤ Baseline Evaluation: Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response, it is necessary to estimate the overall tumor burden at baseline. A sum of the longest diameter for all target lesions (primary tumor, abnormal and measurable lymph nodes) will be calculated and reported as the baseline sum longest diameter. This measurement will be used as the reference by which subsequent measurements will be compared to characterize the objective tumor response.

##### ➤ Response Criteria: Subsequent Evaluation of Target Lesions

Response criteria take into account the measurement of the longest diameter only for all target lesions. Complete response: the disappearance of all target lesions. Partial response: at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. Progressive disease: at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest

diameter recorded since the treatment started, or the appearance of one or more new lesions. Stable disease: neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

➤ Evaluation of Best Overall Response

Those who have non-measurable disease will not be evaluable for response. This includes patients who have had a full resection of their primary tumor via an excisional biopsy. Patients who never began study treatment will also not be included in the assessment of response. Those who receive a minimum of one week of the planned treatment will be included in the analysis of response. Every effort should be made to document disease progression, even after early discontinuation of treatment. Because of issues such as non-measurable disease at baseline or lack of histologically confirmed complete responses, progression free survival is an additional study endpoint for all patients.

The best overall response is the best response recorded from the start of treatment until disease progression or recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Because response rate is a secondary endpoint, and because the clinical examination is often more revealing than scans, confirmation of objective response by a repeat scan in a short interval following the documentation of an objective response will not be required.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. Because of a concern regarding the potential for poor wound healing in the radiated field, a biopsy will only be done if clinically warranted. The need to determine the difference between a partial and complete response, purely for study documentation, will not be adequate justification for a biopsy. If a biopsy result would alter a clinical decision, it should be considered.

### 9.3 Quality Of Life Assessments

The EORTC QLQ-C30 and QLQ-CR38 will be used ([Appendix V](#)). Data will be entered into the QLQ form in AdvantageEDC. Permission has been granted by the EORTC for use of these instruments for the purpose described in this study.

In addition, anal sphincter function will be evaluated according to the Memorial Sloan-Kettering Cancer Center anal function criteria (MSK-AF) ([Appendix V](#)). Data will be entered into the QLQ form in AdvantageEDC. The score *Excellent* (or 1) corresponds to 1-2 bowel movements per day and no soilage. *Good* (or 2) corresponds to 3-4 bowel movements per day and/or soilage. *Fair* (or 3) corresponds to episodic > 4 bowel movements per day and or moderate soilage. *Poor* (or 4) corresponds to incontinence.

#### **9.4 HPV and Anal Cytology**

Polymerase chain reaction (PCR) will be used to detect type specific HPV from anal swab specimens. Type specific PCR will be used to detect HPV in biopsy specimens. The Bethesda criteria will be utilized to classify anal cytology (anal Pap results) as normal, atypical, low or high grade dysplasia or cancer.



## 10.0 STATISTICAL CONSIDERATIONS

### 10.1 Rate of Accrual

It is estimated that accrual to this study will proceed at the rate of 2 eligible and evaluable patients enrolled per month. The study should require approximately 24 months to complete accrual of the 45 eligible and evaluable patients.

### 10.2 Patient Characteristics

Summary statistics will be used to describe the demographic and baseline characteristics of the study population.

### 10.3 Sample Size Estimation

The primary clinical endpoint is local failure rate at 3 years. This trial is designed to detect whether the addition of cetuximab to standard chemoradiation reduces the local failure rate by at least 50%. It is assumed that the local failure rate is approximately 35% at 3 years. To detect a 50% reduction in the local failure rate with a one-sided 0.10 significance level and power of 0.90, 45 eligible patients will be required. Assuming a 10% ineligibility rate, 50 patients will be enrolled. Local failure is defined as persistence or recurrence of disease in the anal canal and/or regional organs and/or regional lymph nodes after completion of protocol therapy (or progression during therapy).

### 10.4 Safety and Additional Toxicity Analysis

*Safety Analysis and Early Stopping Rule:* Type I, II, or III AEs will be reported in an expedited manner (as defined and described in [section 8.4](#)). The study will be interrupted if the incidence of type I events exceed 5%, the incidence of type II events exceeds 20%, or the incidence of type III events exceeds 20% (with a type I error of 0.05). In R9811, the incidence of grade 4 toxicity in the cisplatin/5-FU arm was as follows (as of June 2004): (a) worst overall toxicity 22% (b) worst non-hematologic 9%, (c) worst skin 9%, gastrointestinal 9%, cardiovascular 1%; there were no treatment related deaths recorded. This trial will be stopped if the number of any type of event equals or exceeds the number outlined in the table below, which would be indicative that true risk of a type I event is at least 5%, or the true risk of a type II or type III event is at least 20% (with a type I error rate of 0.05). The research team will analyze the toxicity data, and the study may reopen after an amendment in the trial designed to reduce toxicity is formulated and submitted to CTEP for review and approval. Toxicity will be analyzed separately in the standard RT group and IMRT group.

No. Patients Treated	No. Patients with Type I Events	No. Patients with Type II Events	No. Patients with Type III Events
1-10	≥ 3	≥ 5	≥ 5
11-20	≥ 4	≥ 8	≥ 8
21-30	≥ 5	≥ 11	≥ 11

*Efficacy Analysis and Early Stopping Rule:* The objective response rate reported in previous phase II trials of cisplatin/5-FU/RT in immunocompetent patients was 95%. In this trial, if an objective response rate of 85% or less is seen in the first 22 evaluable patients, the study investigators will discuss with CTEP whether to continue the study.

*Additional Toxicity Analyses:* A descriptive report of toxicity of AEs will be performed. Additional analyses of toxicity will be performed looking at the group as a whole in order to document the entire scope of toxicity in this patient population. Toxicity will be evaluated by use of the following markers:

- Colostomy rate
- The duration and frequency of any treatment breaks or hospitalizations
- The change in HIV viral load and CD4 levels with therapy or progression to AIDS
- The occurrence of grade 3 or higher late treatment complications
- The occurrence of grade 3 or higher systemic toxicity

A logistic regression analysis will be done to determine if the rate of grade 3 or higher acute toxicity within 90 days of completing protocol therapy is related to baseline CD4 count ( $\geq$ / $<$  200), HIV viral load (detectable or not), nadir CD4 level, use of HAART while on CMT, or radiation dose.

Analysis of variance for repeated measures will be used to evaluate the group for changes from baseline to weeks 12, 26 and 52 with respect to viral load and CD4 as continuous variables.

## **10.5 Efficacy Analysis**

The primary endpoint of the trial is local failure rate at 3 years. Objective response at the completion of treatment is a secondary endpoint. Patients will be classified into two groups for purposes of primary endpoint analysis: failure or no failure at 3 years (in the primary analysis, patients lost to follow-up prior to 3 years will be considered failures). For the secondary endpoint of objective response, patients will be classified as responders (complete or partial responders) and non-responders. The binomial proportion and its 95% confidence interval will be used to estimate the 3-year local failure rate, complete response rate, and overall response rate. Logistic regression analysis will be used to evaluate the effect of baseline characteristics and other covariates with failure rate and response. The efficacy analysis will include patients treated with both conventional RT and IMRT. An exploratory analysis of the primary endpoint (local failure) will be conducted based on the type of radiation received (RT and IMRT); local failure will be monitored continuously for both treatment strata (conventional RT vs. IMRT) throughout the course of the study. The trial may be amended to exclude IMRT if it becomes apparent that IMRT results in inferior disease control or worse toxicity.

The Kaplan-Meier method will be used to evaluate the distribution of response duration, progression-free survival, relapse-free survival, colostomy-free survival, and overall survival. The Cox proportional hazards model will be used to evaluate baseline characteristics and other covariates with respect to these time to event measures. These

analyses will be performed after the study has reached its accrual goal, and the data have sufficiently matured to permit a definitive analysis regarding the primary objective. The following definitions will be used for these analyses: (1) response duration: date objective response first documented until date of progression or relapse [patients who died of causes other than anal cancer are censored at the time of death] (2) progression-free survival: date of registration until date of progression, relapse, or death from any cause, (3) relapse-free survival: date objective response first documented until date of progression, relapse, or death from any cause, (4) colostomy free survival: date of registration (for those without colostomy at registration) until date that colostomy is required, (5) overall survival: date of registration until date of death from any cause.

If there is more than one HIV viral load measurement taken between the time the cancer was detected and treatment was initiated, the first viral load measurement will be used for the purposes of correlating presenting or baseline factors with efficacy outcomes. The final viral load obtained just prior to the initiation of therapy will be used for the purposes of correlating treatment tolerance relative to viral load. This distinction is made as some patients may have a change in antiviral therapy made before CMT for anal cancer is begun. The Wilcoxon signed rank test will be used to evaluate changes from baseline in HIV viral load and CD4 counts. The incidence of opportunistic infections will be estimated using the binomial proportion and its 95% confidence interval. The multivariate analysis will be done to determine if lack of tumor control is related to baseline CD4 count, HIV viral load, tumor stage, use of HAART, or other factors.

#### **10.6 HPV Response and Anal Cytology**

Descriptive statistics will be used to describe the types of HPV found in baseline anal swabs and tissue biopsies, the proportion of cases with each type, and the proportion that remain positive for the same type(s) at week 26 (month 6). See [Appendix VI](#) for details of the HPV detection methods. Similarly, descriptive statistics will be used to describe the proportion of patients with HSIL, LSIL, and normal anal cytology.

#### **10.7 Quality of Life Analysis**

The EORTC QLQ-C30 and QLQ-CR38 are validated instruments. The scoring of the instruments is described in [Appendix V](#). All scores obtained are linearly transformed such that all scales range from 0 to 100. Missing values will be calculated such that if at least half the items from the scale are completed, it will be assumed that the missing items would have been equal to the average of the completed items. Analysis of variance (ANOVA) methods will be used to evaluate changes in quality of life measures with time. Multivariate analysis of variance (MANOVA) will be used to evaluate changes across quality of life measures for the entire group and for each arm. General linear models will be used to evaluate the associations between quality of life measures and the following factors: baseline CD4 (< 200 or > 200), viral load (detectable or not), prior AIDS diagnosis (yes, no), baseline performance status (> 80, < 80), nadir CD4 (< 200 or > 200), or radiation dose (> 55 Gy). A difference with a P-value of < 0.05 will be considered as significant.

## **10.8 AMC Policy for Monitoring of Phase II Trials**

This protocol will follow the AMC's policy for data monitoring (see [Appendix X](#)).

## **11.0 ETHICAL AND REGULATORY CONSIDERATIONS**

### **11.1 Publication of Research Findings**

Publication of the results of this trial will be governed by AMC policies.

### **11.2 Discipline Review**

All pathology and cytology will be evaluated by a single pathologist at a central location ([Appendix VI](#)). This will not be done in real time. This will include a review of the pre-treatment biopsy and anal Pap tests. Radiation therapy quality control will be performed by QARC (as outlined in [section 5.5](#)):

**Quality Assurance Review Center**

272 West Exchange Street, Suite 101

Providence, RI 02903-1025

Phone: (401) 454-4301/Fax: (401) 454-4683

URL: [www.qarc.org](http://www.qarc.org)

### **11.3 Institutional Review Board (IRB) Review and Informed Consent**

This protocol and the informed consent document ([Appendix VII](#)) and any subsequent modifications will be reviewed and approved by the IRB or Ethics Committee responsible for oversight of the study. Written informed consent will be obtained from the subject. The subject must be able to understand the nature, significance and risks associated with the study. The informed consent will describe the purpose of the study, the procedures to be followed and the risks and benefits of participation. A copy of the consent form will be given to the subject.

### **11.4 Subject Confidentiality**

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA, the AMC or the NCI.

### **11.5 Study Discontinuation**

This study may be discontinued at any time by the NCI or the AMC.

### **11.6 Biohazard Containment**

The transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood and blood products. Appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as currently recommended by the Centers for Disease Control.

All infectious specimens will be sent using the II-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations - Packing Instruction 602. Please refer to individual carrier guidelines (e.g., FedEx, Airborne) for specific instructions.

#### **11.7 Women and Minorities**

This is a study being conducted by the NCI sponsored AIDS Malignancy Consortium (AMC). As part of their contractual obligations, each participating site within the AMC and the AMC as a whole are required to assure that the participation of women and minority patients reflects the percentage representation of these populations in their geographic region and, for the AMC, the United States as a whole. As such, it is expected that the representation of patients on this trial will reflect the constitution of the respective populations.

## **12.0 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)**

Not applicable.

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# APPENDIX I: SCHEDULE OF EVALUATIONS

Test/Evaluation	Within 6 weeks	Within 4 weeks	Within 2 weeks	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 12	W 18	W 26	M 9	M 12	M 18, 24, 30	M 36	M 48	M 60
<b>Clinical</b>																					
Medical History			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Review			X																		
Tumor Measurement/Assessment (8)			X										X	X	X	X	X	X	X	X	X
Physical Examination			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cervical PAP smear (9)	X (6 mo.)																				
<b>Laboratory Studies</b>																					
EKG	X																				
CBC with differential, platelets (11)			X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
PT and PTT			X																		
Chemistry Panel (2) and Mg++			X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
CD4/CD8 Lymphocyte Count	X							X				X			X		X		X		X
HIV-1 Plasma RNA	X							X				X			X		X		X		X
Anal swab for HPV, cytology (3)			X (3)												X						
Optional frozen tumor specimen (12)	X (12)																				
Tumor specimen submission (4)	X																				
Pregnancy Test (5)			X	PR N																	
<b>Staging</b>																					
Chest x-ray (or chest CT if indicated)		X											X		X	X	X	X	X	X	
Abdominal/Pelvic CT (or MRI)		X											X		X	X	X	X	X	X	
Endorectal ultrasound (10)		X																			
QOL Survey (3,6)			X (3)					X					X		X		X	X (24 mo.)	X		
ACSR Donation (3, 7)			X (3)																		

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Abbreviations: Within 6, 4, 2 weeks (of registration); W – week; M – months;; mo. - months

See [section 6.4](#) for off-study testing for patients who withdraw from treatment or from study prior to completion (if they are agreeable to testing).

1. HIV seropositivity may have been documented at any time prior to registration.
2. Chemistry panel includes: BUN, creatinine, total and direct bilirubin, AST(SGOT), ALT(SGPT), alkaline phosphatase, albumin, electrolytes (sodium, potassium, chloride, bicarbonate) and serum magnesium.
3. These tests should be performed after consent is obtained because they would not otherwise be performed as part of routine clinical care.
4. See [Appendix VI](#) for submission of baseline diagnostic biopsy specimen confirming diagnosis of anal carcinoma (preferably obtained within 6 weeks of registration). The specimen should be submitted within 4 weeks of registration.
5. A negative serum or urine pregnancy test is required within 14 days prior to registration, and may be repeated PRN by the treating physician if clinically indicated after this time.
6. The EORTC quality of life instruments. (See [Appendix V](#)).
7. After patient has provided a separate consent for ACSR donation.
8. Tumor measurement/assessment by physical examination should be performed within two weeks of registration and at the indicated times in order to monitor response to therapy; biopsy may be indicated after completion of treatment or at a future date if persistent disease or relapse is suspected.
9. A cervical PAP smear should be performed within 6 months of registration for women with a cervix.
10. Suggested but not required to assess disease if available at local institution.
11. If radiation is held due to cytopenia, laboratory monitoring should increase to include twice per week CBC, differential, and platelet count until recovery to an ANC.
12. For patients who consent to optional tumor biopsy for submission of fresh frozen tumor tissue to ACSR (see [Appendix IX](#)).

## APPENDIX II: ANAL CANCER STAGING CRITERIA

From the AJCC Cancer Staging Manual Fifth Edition

### Primary Tumor (T)

<b>TX</b>	Primary tumor cannot be assessed
<b>T0</b>	No evidence of primary tumor
<b>Tis</b>	Carcinoma in situ
<b>T1</b>	Tumor 2 cm or less in greatest dimension. This includes microscopically invasive tumor confirmed histologically but not apparent clinically
<b>T2</b>	Tumor more than 2 cm but not more than 5 cm in greatest dimension
<b>T3</b>	Tumor more than 5 cm in greatest dimension
<b>T4</b>	Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, bladder. Involvement of the sphincter muscle(s) alone is not classified as T4.

### Regional Lymph Nodes (N)

<b>NX</b>	Regional lymph nodes cannot be assessed
<b>N0</b>	No regional lymph node metastasis
<b>N1</b>	Metastasis in perirectal lymph nodes(s)
<b>N2</b>	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
<b>N3</b>	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

### Distant Metastasis (M)

<b>MX</b>	Distant metastasis cannot be assessed
<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis

### Stage Grouping

<b>Stage 0</b>	Tis	N0	M0
<b>Stage I</b>	T1	N0	M0
<b>Stage II</b>	T2	N0	M0
	T3	N0	M0
<b>Stage IIIA</b>	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
<b>Stage IIIB</b>	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
<b>Stage IV</b>	Any T	Any N	M1

### APPENDIX III: KARNOFSKY PERFORMANCE SCALE

Able to carry on normal activity; no special care is needed	<b>100</b>	Normal; no complaints; no evidence of disease
	<b>90</b>	Able to carry on normal activity; minor signs or symptoms of disease
	<b>80</b>	Normal activity with effort; some signs of symptoms of disease
Unable to work, able to live at home and care for most personal needs; a varying amount of assistance is needed	<b>70</b>	Cares for self; unable to carry on normal activity or to do active work
	<b>60</b>	Requires occasional assistance but is able to care for most of his needs
	<b>50</b>	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	<b>40</b>	Disabled; requires special care and assistance
	<b>30</b>	Severely disabled; hospitalization is indicated although death is not imminent
	<b>20</b>	Very sick; hospitalization necessary; active supportive treatment is necessary
	<b>10</b>	Moribund; fatal processes progressing rapidly
	<b>0</b>	Dead

# APPENDIX IV: RTOG/EORTC LATE RADIATION MORBIDITY SCORING SCHEME

## Use for Adverse Event Occurring Greater Than 90 Days After Radiation Therapy

Grade					
Adverse Event	0	1	2	3	4
Bladder-Late RT Morbidity Scoring	No change from baseline	Slight epithelial atrophy/minor telangiectasia (microscopic hematuria)	Moderate frequency/generalized telangiectasia/intermittent macroscopic hematuria	Severe frequency and dysuria/severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 mL)	Necrosis/contracted bladder (capacity <100 mL)/severe hemorrhagic cystitis
Bone-Late RT Morbidity Scoring	No change from baseline	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/spontaneous fracture
Brain-Late RT Morbidity Scoring	No change from baseline	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; coma
Esophagus-Late RT Morbidity Scoring	No change from baseline	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis/perforation; fistula
Eye-Late RT Morbidity Scoring	No change from baseline	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment; severe glaucoma	Panophthalmitis; blindness



Grade					
Adverse Event	0	1	2	3	4
Heart- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia >110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low QRS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade/ severe heart failure/severe constrictive pericarditis
Joint- Late RT Morbidity Scoring	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis/ complete fixation
Kidney- Late RT Morbidity Scoring	No change from baseline	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25 - 35 mg%; creatinine 1.5 - 2.0 mg%; creatinine clearance >75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea >36 - 60 mg%; creatinine clearance >50 - 74%	Severe albuminuria; severe hypertension; persistent anemia (<10 g%); severe renal failure; urea >60 mg%; creatinine >4 mg%; creatinine clearance <50%	Malignant hypertension; uremic coma/urea >100%
Larynx- Late RT Morbidity Scoring	No change from baseline	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis
Liver- Late RT Morbidity Scoring	No change from baseline	Mild lassitude; nausea; dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis/hepatic coma or encephalopathy

Grade					
Adverse Event	0	1	2	3	4
Lung- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency/ continuous O <sub>2</sub> /assisted ventilation
Mucous membrane- Late RT Morbidity Scoring	No change from baseline	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucus	Marked atrophy with complete dryness; severe telangiectasia	Ulceration
Salivary glands- Late RT Morbidity Scoring	No change from baseline	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Skin- Late RT Morbidity Scoring	No change from baseline	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Small/Large intestine- Late RT Morbidity Scoring	No change from baseline	Mild diarrhea; mild cramping; bowel movement 5 x daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5 x daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/ perforation fistula
Spinal cord- Late RT Morbidity Scoring	No change from baseline	Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurological findings at or below cord level treatment	Mono-, para-, quadriplegia
Subcutaneous tissue- Late RT Morbidity Scoring	No change from baseline	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture >10% linear measurement	Necrosis
Radiation - Other (Specify, _____)	None	Mild	Moderate	Severe	Life-threatening or disabling

## APPENDIX V: QUALITY OF LIFE INSTRUMENTS

The following pages include:

- 1) The EORTC Instruments (QLQ-C30 and QLQ-CR38)
- 2) Supplemental Quality of Life Questions, including The Memorial Sloan Kettering Anal Function Scale (MSK-AF)
- 3) Scoring procedures for the EORTC Instruments



### EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: \_\_\_\_\_

Your birthdate (Month, Day, Year): \_\_\_\_/\_\_\_\_/\_\_\_\_

Today's date (Month, Day, Year): \_\_\_\_/\_\_\_\_/\_\_\_\_

	NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
<b>During the past week:</b>				
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4

	NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
<b>During the past week:</b>				
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4

	NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall **health** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall **quality of life** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent



## EORTC QLQ – CR38

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

	NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH
<b>During the past week:</b>				
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Did you have pain when you urinated?	1	2	3	4
34. Did you have a bloated feeling in your abdomen?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks?	1	2	3	4
37. Were you bothered by gas (flatulence)?	1	2	3	4
38. Did you belch?	1	2	3	4
39. Have you lost weight?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you had thin or lifeless hair as a result of your disease or treatment?	1	2	3	4
42. Did food and drink taste different from usual?	1	2	3	4
43. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
44. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
45. Have you been dissatisfied with your body?	1	2	3	4

	NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH
46. Were you worried about your health in the future?	1	2	3	4
<b>During the past <u>four</u> weeks:</b>				
47. To what extent were you interested in sex?	1	2	3	4
48. To what extent were you sexually active (with or without intercourse)?	1	2	3	4
49. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4
<b>During the past week:</b>				
<b>For men only:</b>				
50. Did you have difficulty getting or maintaining an erection?	1	2	3	4
51. Did you have problems with ejaculation? (i. e., a so called dry ejaculate?)	1	2	3	4
<b>Only for women who have had intercourse:</b>				
52. Did you have a dry vagina during intercourse?	1	2	3	4
53. Did you have pain during intercourse?	1	2	3	4
<b>During the past week:</b>				
<b>Only for patients WITHOUT a stoma (colostomy bag):</b>				
55. Did you have frequent bowel movements during the day?	1	2	3	4
56. Did you have frequent bowel movements during the night?	1	2	3	4
57. Did you feel the urge to move your bowels without actually producing any stools?	1	2	3	4
58. Have you had any unintentional release of stools?	1	2	3	4
59. Have you had blood with your stools?	1	2	3	4
60. Have you had difficulty in moving your bowels?	1	2	3	4

	NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH
61. Have your bowel movements been painful?	1	2	3	4
<b>Only for patients WITH a stoma (colostomy bag):</b>				
62. Were you afraid that other people would be able to hear your stoma?	1	2	3	4
63. Were you afraid that other people would be able to smell your stools?	1	2	3	4
64. Were you worried about possible leakage from the stoma bags?	1	2	3	4
65. Did you have problems with caring for your stoma?	1	2	3	4
66. Was your skin around the stoma irritated?	1	2	3	4
67. Did you feel embarrassed because of your stoma?	1	2	3	4
68. Did you feel less complete because of your stoma?	1	2	3	4



### Supplemental Quality of Life Questions

1. How satisfied are you with your current degree of anal or anal / rectal function, on a scale of 1-10 with 1 being totally dissatisfied to 10 totally satisfied?

1      2      3      4      5      6      7      8      9      10

Totally Dissatisfied

Totally Satisfied

2. MEMORIAL SLOAN KETTERING ANAL FUNCTION SCALE

How well does your anus function?

**1** = Excellent; Typically 1-2 bowel movements per day and no soilage.

**2** = Good; Typically 3-4 bowel movements per day and / or mild soilage.

**3** = Fair; > 4 bowel movements a day at least at times and / or moderate soilage.

**4** = Poor; Incontinence.

## **SCORING PROCEDURES FOR THE EORTC COLORECTAL CANCER MODULE (EORTC QLQ-CR38)**

### **I. Functional scales**

The questionnaire includes 4 functional scales/single items:

- Body image (BI)
- Sexual functioning (SX)
- Sexual enjoyment (SE)
- Future perspective (FU)

These 4 scales are all constructed in a similar manner: (1) the raw scores for the individual items within a scale are first summed, and then divided by the number of items in the scale; and (2) these scale scores are then linearly transformed such that all scales range from 0 to 100, with a higher scale score representing a higher level of functioning.

The following are the scoring algorithms for the 4 functional scales, including the SPSS computational language.

#### **Body Image (Questionnaire items 43-45)**

1. Compute an additive scale (BI) by adding the questionnaire items 43-45 and dividing this sum by the number of items (3):  
$$\text{COMPUTE BI} = (\text{Q43} + \text{Q44} + \text{Q45}) / 3$$
2. Carry out a linear transformation to convert the scale (BI) to a 0-100 scale (XBI):  
$$\text{COMPUTE XBI} = 100 - ((\text{BI} - 1) * 100 / 3)$$

#### **Future Perspective (Questionnaire item 46)**

$$\text{COMPUTE FU} = \text{Q46}$$
$$\text{COMPUTE XFU} = 100 - ((\text{FU} - 1) * 100 / 3)$$

#### **Sexual Functioning (Questionnaire items 47 and 48)**

1. Compute an additive scale (SX) by adding the questionnaire items 47 and 48 and dividing this sum by the number of items (2):  
$$\text{COMPUTE SX} = (\text{Q47} + \text{Q48}) / 2$$
2. Carry out a linear transformation to convert the scale (SX) to a 0-100 scale (XSX):  
$$\text{COMPUTE XSX} = (\text{SX} - 1) * 100 / 3$$

#### **Sexual Enjoyment (Questionnaire item 49)**

$$\text{COMPUTE SE} = \text{Q49}$$
$$\text{COMPUTE XSE} = (\text{SE} - 1) * 100 / 3$$

## II. Symptom Scales/Items

The questionnaire includes a number of multi-item scales and single items assessing a range of symptoms common among patients with colorectal cancer. These scales and single items are linearly transformed such that all scales/items range from 0-100, with a higher score representing a higher level of symptomatology.

- Micturition problems (MI)
- Chemotherapy side effects (CT)
- Symptoms in the area of the gastro-intestinal tract (GI)
- Male sexual problems (MSX)
- Female sexual problems (FSX)
- Defaecation problems (DF)
- Stoma-related problems (STO)
- Weight loss (WL)

### **Micturition Problems (Questionnaire items 31-33)**

1. Compute an additive scale (MI) by adding the questionnaire items 31-33 and dividing this sum by the number of items (3):  
$$\text{COMPUTE MI} = (Q31+Q32+Q33)/3$$
2. Carry out a linear transformation to convert the scale (MI) to a 0-100 scale (XMI):  
$$\text{COMPUTE XMI} = (MI-1)*100/3$$

### **Chemotherapy Side-effects (Questionnaire items 40-42)**

1. Compute an additive scale (CT) by adding the questionnaire items 40-42 and dividing this sum by the number of items (3):  
$$\text{COMPUTE CT} = (Q40+Q41+Q42)/3$$
2. Carry out a linear transformation to convert the scale (CT) to a 0-100 scale (XCT):  
$$\text{COMPUTE XCT} = (CT-1)*100/3$$

### **Symptoms in the Area of the Gastro-intestinal Tract (Questionnaire items 34-38)**

1. Compute an additive scale (GI) by adding the questionnaire items 34-38 and dividing this sum by the number of items (5):  
$$\text{COMPUTE GI} = (Q34+Q35+Q36+Q37+Q38)/5$$
2. Carry out a linear transformation to convert the scale (GI) to a 0-100 scale (XGI):  
$$\text{COMPUTE XGI} = (GI-1)*100/3$$

### **Male Sexual Problems (Questionnaire items 50 and 51)**

1. Compute an additive scale (MSX) by adding the questionnaire items 50 and 51 and dividing this sum by the number of items (2):  
$$\text{COMPUTE MSX} = (Q50+Q51)/2$$

2. Carry out a linear transformation to convert the scale (MSX) to a 0-100 scale (XMSX):  

$$\text{COMPUTE XMSX} = (\text{MSX}-1)*100/3)$$

#### **Female Sexual Problems (Questionnaire items 52 and 53)**

1. Compute an additive scale (FSX) by adding the questionnaire items 52 and 53 and dividing this sum by the number of items (2):  

$$\text{COMPUTE FSX} = (\text{Q52}+\text{Q53})/2$$
2. Carry out a linear transformation to convert the scale (FSX) to a 0-100 scale (XFSX):  

$$\text{COMPUTE XFSX} = (\text{FSX}-1)*100/3)$$

#### **Defecation Problems (Questionnaire items 55 -61)**

1. Compute an additive scale (DF) by adding the questionnaire items 55-61 and dividing this sum by the number of items (7):  

$$\text{COMPUTE DF} = (\text{Q55}+\text{Q56}+\text{Q57}+\text{Q58}+\text{Q59}+\text{Q60}+\text{Q61})/7$$
2. Carry out a linear transformation to convert the scale (DF) to a 0-100 scale (XDF):  

$$\text{COMPUTE XDF} = (\text{DF}-1)*100/3)$$

#### **Stoma-related Problems (Questionnaire items 62-68)**

1. Compute an additive scale (STO) by adding the questionnaire items 62-68 and dividing this sum by the number of items (7):  

$$\text{COMPUTE STO} = (\text{Q62}+\text{Q63}+\text{Q64}+\text{Q65}+\text{Q66}+\text{Q67}+\text{Q68})/7$$
2. Carry out a linear transformation to convert the scale (STO) to a 0-100 scale (XSTO):  

$$\text{COMPUTE XSTO} = (\text{STO}-1)*100/3)$$

#### **Weight loss (Questionnaire item 39)**

$$\text{COMPUTE WL} = \text{Q39}$$

$$\text{COMPUTE XWL} = (\text{WL}-1)*100/3$$

Further inquiries regarding the scoring algorithms for the EORTC QLQ-C38 can be directed to: Dr. Mirjam Sprangers, Department of Medical Psychology, Academic Medical Hospital, University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands. Telephone: +31-20-5664641; Telefax: +31-20-5669104.

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## SCORING PROCEDURES FOR EORTC QLQ-C30 version 3.0

**Table 1: Scoring the QLQ-C30 version 3.0**

	Scale	Number of Items	Item Range*	Version 3.0 Item Numbers	Function Scales
<b>Global Health Status / QOL</b>					
Global health status/QOL (revised) <sup>†</sup>	QL2	2	6	29, 30	
<b>Functional Scales</b>					
Physical functioning (revised) <sup>†</sup>	PF2	5	3	1 to 5	F
Role functioning (revised) <sup>†</sup>	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
<b>Symptom Scales / Items</b>					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

\* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix “2” – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + \dots + I_n) / n$$

Then, for **Functional scales**:

$$Score = \left\{ 1 - \frac{(RS - 1)}{range} \right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QOL**:

<b>Examples:</b>	
Emotional Functioning	$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24}) / 4$ $EF\ Score = \{1 - (RawScore - 1) / 3\} \times 100$
Fatigue	$RawScore = (Q_{10} + Q_{12} + Q_{18}) / 3$ $FA\ Score = \{(RawScore - 1) / 3\} \times 100$

$$Score = \{(RS - 1) / range\} \times 100$$

## APPENDIX VI: HPV, CYTOLOGY & PATHOLOGY SPECIMENS

### **AMC-045: Phase II Trial of Combined Modality Therapy plus Cetuximab in HIV-Associated Anal Carcinoma**

#### **SPECIMEN REQUIREMENTS**

All specimens will be reviewed at UCSF and must be submitted within 30 days of study enrollment. The tissue block along with a copy of the surgical pathology report should be sent. If the block is not available, a representative H & E stained section and ten unstained slides should be submitted. All materials will be retained unless return is specifically requested. Tissue will be evaluated for histology as demonstrated by H & E staining, HPV detection and typing, and microarray DNA expression. Other studies might be added at a later point in time as additional correlative science studies are developed. These evaluations will not be done in real time. The collaborating pathologist will be Dr. Teresa M. Darragh, M.D., Professor of Clinical Pathology, UCSF/ Mt. Zion Medical Center, Depts. of Pathology and OB/Gyn, Box 1785, 1600 Divisadero Street, Room B221, San Francisco, CA 94115, phone: 415.353.7861, Fax: 415.353.7676, Email: [darragh@itsa.ucsf.edu](mailto:darragh@itsa.ucsf.edu).

At baseline, an anogenital examination will be performed for HPV testing and anal cytology. To obtain the cytology specimen, a swab will be placed in the anus (another obtained from the cervix if applicable) for several seconds, withdrawn, immediately immersed in the Cytoc Thinprep bottle and agitated vigorously to remove the cells. Discard the swab, close the bottle tightly and send it to the UCSF Pathology Department. This will be evaluated for cytology and an aliquot will be removed for PCR studies of the HPV types(s) present.

#### **SAMPLE LABELING**

Protocol #: AMC 045

AMC Patient ID #

Study period as described by week number

Date and time of specimen collection.

Specimen type: “Anal swab” or “Tissue block”

Specimen purpose: “Cytology” or “Pathology”

#### **PRECAUTIONS**

All specimens are to be considered biohazard material, as they originate from HIV infected patients. This should be designated by use of a “Universal Precautions” label.

## **SPECIMEN DELIVERY**

These samples should be shipped using the AMC Operations Center FedEx [REDACTED]  
[REDACTED]

All specimens should be sent at room temperature immediately to:

Dr. Joel Palefsky's Laboratory  
c/o Maria Da Costa  
University of California, San Francisco  
513 Parnassus Ave., Room S-420  
San Francisco, CA 94143  
Tel: 415-476-8885

## **RECORD OF SPECIMENS**

This study will track specimens via GlobalTrace<sup>SM</sup>, a component of the AMC AdvantageEDC<sup>SM</sup> system. The GlobalTrace<sup>SM</sup> shipment manifest must accompany all specimen shipments.

## APPENDIX VII: INFORMED CONSENT

### **AMC-045: Phase II Trial of Combined Modality Therapy plus Cetuximab in HIV-Associated Anal Carcinoma**

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

You are being asked to take part in this study because you have recently been diagnosed with cancer of the anus for which radiation and chemotherapy together have been recommended to you, in an attempt to cure this cancer. You must also be an adult infected with the AIDS virus, HIV, but otherwise be in fairly good health with adequate bone marrow, kidney and liver function.

#### **WHY IS THIS STUDY BEING DONE?**

The main purpose of this study is to determine the effectiveness of standard chemotherapy and radiation when combined with cetuximab for anal cancer. Although there is much information regarding the specific treatment used for anal cancer used in this study, there is less information regarding how patients with anal cancer and HIV infection respond to the treatment and what side effects they have as a result of the treatment. A standard treatment for patients with anal carcinoma not associated with HIV infection includes treatment with chemotherapy plus radiation therapy. The chemotherapy drugs typically used with radiation therapy include mitomycin-C and 5-fluorouracil (5-FU), although recent studies have suggested that cisplatin and 5-FU may be as effective and associated with fewer side effects. In this study, cisplatin and 5-FU will be the chemotherapy regimen used. In addition, we will utilize a drug called cetuximab, which is approved for the treatment of colon cancer. Cetuximab is a monoclonal antibody, or protein, that is directed against a target on the surface of the cancer cell. The target is called "epidermal growth factor receptor", or EGFR. Cetuximab has been shown to enhance the effectiveness of cisplatin and radiation therapy in other types of cancer.

During this study, you will be followed closely during and after therapy to see how well your cancer is controlled by the radiation and chemotherapy treatment, how the treatment affects your HIV illness, what side effects you have, and how you tolerate the treatment.

#### **HOW MANY PEOPLE WILL TAKE PART IN THE STUDY**

About 46 people will take part in this study.

#### **WHAT IS INVOLVED IN THE STUDY?**

You have already been diagnosed with anal cancer and are already known to be HIV-positive or have just found this out. Radiation and chemotherapy given together (combined modality therapy or "CMT") has been recommended as the best treatment for your condition. A standard treatment



for patients with anal carcinoma not associated with HIV infection includes treatment with chemotherapy plus radiation therapy. The chemotherapy drugs typically used with radiation therapy include mitomycin-C and 5-fluorouracil (5-FU), although recent studies have suggested that cisplatin and 5-FU may be as effective and associated with fewer side effects. In this study, cisplatin and 5-FU will be the chemotherapy regimen used.

Before being enrolled in this study, you went through a physical examination and other routine tests to determine the size and extent of your cancer. The studies probably included a CT scan or MRI of your pelvis, a CT scan of your abdomen to check the liver, and a chest Xray or CT scan of the chest. If anything suggested that the cancer has spread outside of the pelvis, a biopsy of the area may be needed. If you have cancer that has spread outside of the pelvis, you will not be eligible for this study. You also had a history and physical examination and blood work to see if you are, in general, healthy enough to receive this type of treatment. These are all standard procedures that are routinely done even if you were not going to enter the study. However, the study will need for all of these tests to be done within a defined time, so that the results are all up to date. If too much time has gone by since these were done before the treatment was started, some of these tests and procedures may need to be repeated. You also must enroll in this study before you have received any of the radiation or chemotherapy.

Once you have entered the study, many of the treatments and tests that you need to do are standard. That is, you would be asked to do many of these things even if you were not in this study. Other treatments or tests and procedures are additional and will be done specifically because you are taking part in this study.

If you take part in this study, you will receive the following standard treatments:

- **CHEMOTHERAPY:** You will be under the care of a medical oncologist while receiving chemotherapy. Two chemotherapy drugs will be used. 5-Fluorouracil (5-FU) will be infused continuously over 4 days (96 hours), starting on the day one of treatment (days 1-4). You will also receive a second course of 5-FU, to be started at the fourth week of treatment (days 29-32). Some patients are admitted to the hospital to receive their 5-FU, but it is more commonly given at home with the assistance of home care nursing agency and/or home infusion company. The second chemotherapy drug that you will receive is cisplatin. This is given in the clinic as an IV infusion over 60 minutes on the first of each 5-FU infusion (day 1 and day 29). Additional fluids and medicines (to prevent nausea) will be given on this day, so this will require several hours of time. A large amount of intravenous fluid (3 liters) must be given intravenously, including about 2 liters before cisplatin and about 1 liter after cisplatin. This will take about 6-8 hours to administer. You may receive the treatment in the treatment in the clinic or the hospital in-patient unit, depending upon the standard procedures used by your doctor at his/her particular hospital/clinic. You will also receive a dose of radiation on the day that cisplatin is given. Medications will be given intravenously and/or orally in order to reduce the chance of developing nausea and/or vomiting.

In order to receive this 5-FU at home, a catheter is placed into one of your veins. This is not just a typical IV (intravenous) line but is one that can be left in for a much longer time. There are several choices of catheters that you can discuss with your doctor. Depending on the type

of catheter placed, you may have to take care of it. The two most common choices include a PIC line placed (usually) in your arm or a Porta-Cath placed internally (under the skin) in your chest.

- **CETUXIMAB:** Cetuximab IV will be given 1 week before the cycle 1 chemotherapy begins. Cetuximab will then be given weekly as an IV infusion for 6 consecutive weeks (Days 1, 8, 15, 22, 29, 36, and 43) during the period of chemotherapy and radiation therapy. Therefore, a minimum of 6 and maximum of 8 doses of cetuximab will be given. Cetuximab is usually given over 60-90 minutes, depending upon the dose given. Diphenhydramine (50 mg) is given IV before cetuximab is given to prevent allergic reactions. Diphenhydramine (also called Benadryl) may cause drowsiness. Cetuximab will be held if the radiation therapy is held; this is because it is believed that cetuximab must be given at the same time that radiation therapy is given to improve control of the disease.
- **RADIATION THERAPY:** Treatment will be given every weekday (Monday through Friday), over approximately five to seven weeks in the outpatient setting. Brief treatment breaks are sometimes needed because of side effects, so this can even take a little longer to finish for some patients. The total number of doses that you are prescribed will depend on the size and extent of your tumor at the start of treatment. You will receive this care from a Radiation Oncologist who will work closely with your Medical Oncologist to coordinate the radiation therapy with the chemotherapy. The minimum number of treatments required will be about 28 (which will take a minimum of about 5 weeks to deliver) and the maximum number of treatments required will be about 35 (which will take a minimum of about 7 weeks to deliver). The treatment itself takes only a few minutes to administer. You will have to lie flat on a table for about 5-10 minutes each time that you receive the treatment. The radiation may be held or interrupted by your doctor if you have significant side effects (eg, skin rash, diarrhea, or other side effects)

There are several ways of administering radiation therapy, including the standard technique and a new technique called IMRT (which stands for Intensity Modulated Radiation Therapy). IMRT is an advanced radiation therapy delivery technique that reduces the amount of radiation given to normal tissues, and may therefore reduce unwanted side effects. IMRT tries to lower the amount of radiation that normal tissues receive, while still delivering the desired amount of radiation to your cancer and to the areas that your doctor thinks may have cancer cells, such as lymph nodes. IMRT does this by using multiple, computer-controlled radiation beams aimed at your cancer, while still delivering a radiation dose comparable to standard radiation. There is little information regarding the effectiveness of IMRT in anal cancer, although some radiation oncologists are beginning to gain experience in using it for this condition. It is not known at this time whether IMRT will result in similar control of the cancer. The choice of whether you will receive standard radiation therapy or IMRT will be at the discretion of your treating physicians, and they will discuss whether conventional RT or IMRT is being recommended in your case.

- **SUPPORTIVE CARE:** You will receive the standard supportive care to control side effects as best as possible. Medicines to control or treat infection, pain, nausea, vomiting, diarrhea, dehydration, and low blood counts will be prescribed as needed. You may need blood

transfusions if you become too anemic, intravenous fluids if you become dehydrated, antibiotics if you develop an infection, narcotics to control pain, and other routine, standard treatments. You may need to be hospitalized if you develop serious side effects.

If you take part in this study, you will have the following standard tests and procedures:

- Before beginning treatment, you will have a complete history and physical examination. Additional tests that will be required in blood tests (including T cell count and HIV viral load, and pregnancy test for women), and electrocardiogram, a chest x-ray, and CT scans and/or MRI to adequately stage the disease. In some cases, a bone scan may be needed if you have symptoms suggesting that the cancer has spread to the bone (bone pain). Your doctor may also recommend an endorectal ultrasound in order to determine whether there is extension of the tumor beyond the anus; this procedure involves insertion of a small probe in the anal canal. All of these tests are considered part of routine medical care for someone with your diagnosis.
- During the course of treatment, you will be seen at your doctor's office once per week for a brief check of how you are doing, what medicines you are taking, and what side effects you are having. Blood tests will also be done regularly.
- At about three months after the start of treatment, you will have a CXR, and CT scan of the abdomen and pelvis, or comparable tests to see how your cancer responded to treatment.
- Once treatment is finished, you will be seen and have blood taken approximately every six weeks, then every three months, then eventually every six to twelve months for a total of five years.
- Additional tests will be repeated as necessary if your cancer is ever suspected of returning.

If you take part in this study, there will be extra tests and procedures, in addition to the standard tests and procedures:

- The tissue that was obtained at the time that the anal cancer was diagnosed (the biopsy) will be stored for research tests. If there is not enough tissue available from this biopsy, another biopsy may be requested before treatment begins. However, this is optional and may only be a needle biopsy. It should not require surgery.
- Before treatment begins, a swab will be inserted briefly into your anus. This is sent to a research laboratory to be tested for HPV (human papillomavirus), the most common cause of anal cancer. The specific type of HPV will be identified. A second swab will be obtained for a Pap smear. This also will be sent to the research laboratory. The Pap smear test will look to see if you have any dysplastic cells. These are not cancer cells but can sometimes be a precursor to cancer. This procedure will be repeated at 6 months. You will not be billed for the HPV test or Pap test.
- If your treatment center has the ability to perform an examination of your anus using high resolution anoscopy (which provides a magnification view of the anal surface), this will be done to more clearly examine the anal canal before treatment begins and at 6 months.
- Quality of life surveys will be performed at several time points. This survey will include a series of questions about how you feel using multiple choice questions and answers. The survey will be given before treatment, and at 3, 6, 12, 24, and 36 months after beginning treatment.

## **HOW LONG WILL I BE IN THE STUDY?**

The treatment program outlined in this trial will take approximately three months to complete. After you complete the chemotherapy and irradiation, your doctor will continue to follow you and request additional tests at 3, 6, 9, 12, 18, 24, 30, 36, 48, and 60 months after treatment is initiated.

You can withdraw your consent at any time. If you request that the treatment be discontinued because of side effects or another reason, your doctor would still need to evaluate you at periodic intervals to monitor the status of the cancer and any early or late side effects you may have. However, you also have the right to withdraw consent for monitoring the status of your cancer at any time.

## **WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for the following side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that are not predicted and other very rare side effects that are known but not included in this list. Other drugs will be given to lessen side effects and discomfort. Many side effects go away shortly after the treatment is stopped, but in some cases side effects can be serious or long lasting or permanent.

### **Chemotherapy (5-FU and Cisplatin)**

Common (likely) side effects of 5-FU or cisplatin include:

- Hair loss
- Mouth sores and/or soreness of the throat
- Diarrhea with cramping and/or bleeding
- Nausea and vomiting, reduced appetite, weight loss and a change in taste
- Low blood cell counts including white cells, red cells (anemia) and platelets
- Decreased magnesium in the blood – this may also be caused by cisplatin: it may result in muscle weakness and cramps
- Loss of energy
- Kidney injury especially if the kidney function is already poor before treatment or if you become dehydrated during therapy. This typically resolves but can be long lasting. It can be worsened by repeated doses of cisplatin.
- Nerve injury which most often is a peripheral neuropathy causing numbness or discomfort in the hands and feet. This generally improves with time but at times can be permanent.
- Hearing loss or ringing in the ears. As above, this generally improves with time but can at times be permanent.
- Reproductive risks: Since 5-FU and cisplatin, and radiation therapy, can affect an unborn baby, you should not become pregnant or father a baby while receiving this therapy. You should not nurse your baby while receiving this therapy. Ask about counseling and more information about preventing pregnancy.
- This therapy can also cause infertility (sterility) so chances for a future pregnancy will be reduced. Ask about more information about ways to preserve fertility

Unlikely side effects of 5-FU or cisplatin include:

- Sensitivity to sunlight
- Skin rash, other nail and skin changes, hair loss
- Tightening of the tear ducts
- Darkening of the vein used for infusion
- Allergic reactions

Very unlikely but serious side effects of 5-FU or cisplatin include:

- Chest pain, heart attack or other heart abnormalities
- Confusion or other neurologic problems including seizures
- Severe diarrhea due to damage of the bowel which can, in rare cases, can lead to death
- Severe drops in the blood counts, which if associated with an infection, could lead to death
- Eye damage
- Loss of muscle or nerve function

### **Cetuximab**

#### **Likely:**

- Diarrhea
- Nausea or the urge to vomit
- Fatigue or tiredness
- Fever
- Headache or head pain
- Dry skin
- Acne
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)

#### **Less Likely:**

- Lack of enough red blood cells (anemia)
- Inflammation (swelling and redness) of the skin of outer ear and canal
- Noise in the ears, such as ringing, buzzing, roaring, clicking
- Inflammation (swelling and redness) of the conjunctiva (the outermost layer of the eye and the inner surface of the eyelids). Commonly called "pink eye".
- Dry eye
- Inflammation (swelling and redness) of the middle layer of the eye (uvea)
- Excessive tearing in the eyes
- Belly pain
- Inflammation (swelling and redness) of the lip
- Constipation
- Dry mouth
- Heartburn
- Irritation or sores in the lining of the mouth
- Vomiting
- Chills

- Swelling of the arms and/or legs
- Flu-type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Dehydration (when your body does not have as much water and fluid as it should)
- Decreased blood level of calcium
- Decreased blood level of magnesium
- Joint pain
- Back pain
- Muscle pain
- Fainting
- Stuffy or runny nose, sneezing
- Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath
- Cough
- Shortness of breath
- Hoarseness
- Hair loss
- Loss of some or all of the finger or toenails
- Increased skin sensitivity to sunlight
- Itching
- Area of bleeding within the skin causing a reddish purple discoloration
- Sore or destruction of skin
- Hives
- Low blood pressure
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

**Rare but Serious:**

- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Inflammation of the lining of the brain and spinal cord
- Inflammation of the lungs that may cause difficulty breathing and can be life-threatening
- Fluid build-up in the lungs that is not due to a heart problem that can be life-threatening

- Swelling and redness of the skin on the palms of the hands and soles of the feet

#### **Also Reported on Clinical Trials of Cetuximab:**

- Rare incidents of heart problems such as chest pain, decreased heart function, and injury to the heart muscle have been observed in clinical trials with cetuximab in combination with 5-FU containing chemotherapies. Cardiac site effects are known to occur with 5-FU; however, we do not know at this time whether the addition of cetuximab to 5-FU increases the risk of these events.
- Heart failure due to heart attack and abnormal heart rhythm, and sudden death has occurred in patients who received cetuximab in combination with radiation therapy.

***It is recommended that you wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can worsen any skin reactions that may occur.***

#### **Reproductive Risks and Breast Feeding:**

Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study, or up to 60 days after the last dose of cetuximab. You should not nurse your baby while on this study, or up to 60 days after the last dose of cetuximab. You may ask your doctor about counseling and more information about preventing pregnancy.

#### **Radiation therapy given to the pelvis and anus**

Common (likely) side effects of radiation include:

- A mild skin burn will always develop but sometimes this can progress to blisters, peeling of the skin, and oozing of the tissues. This will affect the anus, the skin around the anus and possible the skin over the groin, scrotum and penis. This is uncomfortable and can be quite painful when sores develop.
- Diarrhea
- Low white blood cell count, anemia
- Fatigue
- Loss of hair in the groin which may be permanent
- Even after the visible damage of radiation has healed, tissue healing may be slow or incomplete in this area. This means that injury to this area (a biopsy procedure for instance) can be slow to heal even years later.
- Some patients do not return to normal sexual function. Radiation therapy to this area of the body may lead to problems with an erection, ejaculation, or may reduce your ability to have intercourse.

Unlikely but serious side effects of radiation include:

- Long lasting injury to the anus resulting in chronic pain, non-healing open ulcers, or difficulty controlling bowel movements. Sometimes a temporary colostomy (surgical diversion of the bowel through the wall of the abdomen, emptying into a bag) is needed or even a permanent colostomy with the surgical removal of the anus is required.

For more information about risks and side effects, ask the researcher or contact \_\_\_\_\_ at \_\_\_\_\_.

## **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there is no certainty of a direct medical benefit for you. We hope that adding cetuximab to standard therapy will improve our ability to control the disease. We hope the information learned from this study will benefit other patients with anal cancer in the future.

## **WHAT OTHER OPTIONS ARE THERE?**

Instead of being in this study, you have these options:

- You may receive radiation therapy and chemotherapy (combined modality therapy) even if you do not take part in this study.
- You may receive no therapy at this time with standard of care to help you feel more comfortable.
- You may receive surgery to remove the anal cancer, without chemotherapy and radiation or with reduced doses of chemotherapy and radiation.

Please talk to your regular doctor about these and other options.

## **WHAT ABOUT CONFIDENTIALITY?**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the AMC Operations Center, National Cancer Institute, Food and Drug Administration (FDA), the company that will provide cetuximab (Bristol-Myers).

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally-funded projects or for information that must be disclosed in order to meet the requirements of the FDA.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this



research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

## **WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Most of the care (radiation therapy and chemotherapy) will be charged to your insurance company because this care is considered standard care. The drug cetuximab will be provided to you at no cost unless, during the study, cetuximab becomes commercially available for this condition. In that case you may have to pay for the amount of drug needed to complete the study. Please ask about any expected added costs or insurance problems

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

## **WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

## **WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

For questions about the study or a research-related injury, contact the researcher \_\_\_\_\_ at \_\_\_\_\_.

For questions about your rights as a research participant, contact the \_\_\_\_\_ Institutional Review Board (which is a group of people who review the research to protect your rights) at \_\_\_\_\_.

## **CONSENT FOR THE USE OF TISSUE SPECIMENS**

### **About Using Tissue for Research:**

You have had a biopsy (or surgery) in order to confirm your cancer diagnosis. This tissue is normally stored in a local pathology laboratory. We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. This tissue will only be given to researchers

approved by the AIDS Malignancy Consortium (AMC). Any research done on the tissue must also be approved by the researcher's Institutional Review Board (IRB).

The research that may be done with your tissue will probably not help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

**Things to Think About:**

The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care and you may still take part in the AMC study.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want us to use your tissue. Then the tissue will no longer be used for research.

In the future, people who do research may need to know more about your health. When the AMC gives them reports about your health, it will not give them your name, address, or phone number.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. You will not be paid for allowing your leftover tissue to be used in research even though the research done with your tissue may help to develop new products in the future.

**Benefits:**

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, how to treat them, and how to cure them.

**Risks:**

There are very few risks to you. The greatest risk is the release of information from your health records. The AMC will protect your records so that your name will be kept private. The chance that this information will be given to someone else is very small.

In addition to the research you are consenting to under this study, other researchers at this or other institutions may wish to study the samples in future research. These samples, taken from your body, would be able to be linked back to you for the purpose of the study only. At this time, the researcher does not know what the future studies will be. Your specimens may also be submitted to a tissue/cell/DNA bank. The specimens may be kept for a long time, possibly up to 50 years. Information about you may be shared with other researchers who will keep the information confidential, as stated in this consent.

**Making Your Choice:**

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." No matter what you decide to do, it will not affect your care. You can participate in the treatment part of the study without participating in all or part of the tissue research studies. If you have any questions, please talk to your doctor or nurse, or call our research review board at \_\_\_\_\_.

***I agree to have the following specimens sent for future studies:***

Specimen from diagnostic biopsy (this has already been performed and requires no additional procedures)

Yes \_\_\_ No \_\_\_

Anal swab specimen (this requires putting an anal swab in the anal canal)

Yes \_\_\_ No \_\_\_

An additional tumor biopsy in order to freeze and store the tissue (this requires another biopsy to be done)

Yes \_\_\_ No \_\_\_

If you have checked YES in response to any of the following questions, please also answer the following questions:

1. Your tissue may be kept for use in research to learn about, prevent, treat, or cure cancer.

Yes \_\_\_ No \_\_\_

2. Your tissue may be kept for research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease).

Yes \_\_\_ No \_\_\_

3. Your doctor (or someone from the AMC) may contact you in the future to ask you to take part in more research.

Yes \_\_\_ No \_\_\_

You have read all of the above, asked questions and received answers concerning areas that you did not understand. You willingly agree or disagree to allow your blood and/or tissue to be stored for future research.

**WHERE CAN I GET MORE INFORMATION?**

You may call the NCI's Cancer Information Service at

1 800 4 CANCER (1 800 422 6237) or TTY: 1 800 332 8615

Visit the NCI's Web sites

\*CancerTrials: comprehensive clinical trials information <http://cancertrials.nci.nih.gov>.

\*CancerNet: accurate cancer information including PDQ <http://cancernet.nci.nih.gov>.

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

**SIGNATURE**

I agree to take part in this study.

Participant \_\_\_\_\_

Date \_\_\_\_\_

## APPENDIX VIII: ACSR INFORMED CONSENT

### AIDS Cancer Specimen Resource (ACSR)

#### INTRODUCTION

You are being asked to donate tissue for research. Before you decide to be a part of this research study, you need to understand the risks and benefits so that you can make an informed decision. This is known as informed consent.

This consent form provides information about the study, which has been explained, to you. Once you understand the study and the tests it requires, you will be asked to sign this form if you want to take part in the study. Your decision to take part in the study is voluntary. This means that you are free to choose if you will take part in the study.

#### PURPOSE AND BACKGROUND

The National Cancer Institute (NCI) has set up a Bank for tissues and biological fluids from HIV-positive and HIV-negative individuals in order to have specimens available for scientists studying malignancies associated with HIV disease. The specific studies for which specimens will be used are unknown at this point and will vary depending on investigators' requests. Only investigators whose studies are reviewed and approved by a committee assembled by the NCI from the scientific community will have access to specimens. Specimens will only be used for the approved study and a progress report will be required. Publications using AIDS Cancer Specimen Resource (ACSR) specimens will also be sent to the NCI.

Individuals who have had biopsies to determine a malignancy are being asked for permission to have some of the tissue taken for the Bank. Only tissue in excess of that required for decision-making will be given to the Bank. If it is determined that my physician needs more of my tissue for additional studies, the Bank will release all of my tissue back to my doctor. No additional tissue will be taken from my body for the Bank. In addition, I am being requested to donate some of my blood to the Bank so that scientists will also be able to look for any deviation that may explain the malignancy. Once these specimens are deposited in the bank, they become the sole property of the Bank and I will no longer have any rights to the specimens.

#### PROCEDURES

If I agree to be in this study, the following will happen:

1. Some of the material from my biopsy for a malignancy will be placed in the Bank.
2. The swabs taken from my anus before the start of treatment and then at six months will be sent to the Bank.
3. My medical chart will be reviewed now and every six months for an indefinite period of time and clinical information will be obtained that could be useful to research investigators. The report of the information retrieved from my medical record that is given to research

investigators will not have my name, or include any information that could personally identify me.

4. Blood will be collected for the Bank. Approximately twenty (20) milliliters of blood (about 4 teaspoons) will be drawn at my next visit to my physician and placed in the Bank.
5. If, during the course of treatment by my physician, it is necessary to perform additional biopsy procedures for diagnostic reasons, I will be asked at that time to consent to having a portion of that specimen sent to the Bank. No additional blood will be drawn at that time.

Participation in this study will not require me to make any additional visits to my doctor or have any additional biopsy specimens taken just for the Bank. The Bank will only receive part of my specimen, and only what is in excess.

## **POSSIBLE RISKS/DISCOMFORTS**

There is a possibility of a bruise and slight pain at the time the blood samples are taken. There is also the possibility of fainting, and infection at the site of the blood draw.

**Treatment and Compensation for Injury:** If you are injured as a result of being in this study, treatment will be available. If you require immediate medical care, you should go to an emergency room. Otherwise, the doctor in charge of the study will take care of you or help you get the care you need. You will be sent a bill for whatever medical care you receive. All or part of your bill may be paid by the sponsor of the research study (according to its agreement with the AIDS Malignancy Clinical Trials Consortium), or by your health insurance. (*Institution*) does not normally provide any form of compensation for injury that might occur from taking part in this research study.

## **POSSIBLE BENEFITS**

It may be that there will be no direct benefit to you by participating in this study. However, there may be possible benefit to medical knowledge and it is hoped that the information gained from the study will help in the treatment of HIV- infected individuals in the future.

## **ALTERNATIVES**

My alternative is not to participate in this study.

## **COSTS**

There will not be any additional cost to me for consenting to participate in this HIV-related malignancy tissue/biological fluids Bank.

## PRIVACY

Your hospital medical records will be confidentially reviewed to obtain clinical information that could be useful to research investigators. However, the report of this information will be coded and my name and/or social security number will not appear anywhere on the report sent to the Bank, so I will not be easily identified. The results of this research will be given to the sponsor, the National Cancer Institute, and may be asked for by the Department of Health and Human Services. In addition, the Committee on Human Research of **(Institution)** may see your records. Except for these people, records from this study will be kept private unless you authorize their release or release is required by law (i.e. court subpoena). Your name or any information, which could personally identify you, will not be used in any published reports about this study.

## QUESTIONS

If I have any questions about the research study, you may contact Dr. (\_\_\_\_\_) at **(Phone Number)** day or night, or the person in charge of the study, the study coordinator at **(Phone Number)**. If you have any questions about your rights as a research subject, you should call **(IRB Representative)**, in **(Institution)** Office of Human Research at **(Phone Number)**. **(IRB Representative)** is your representative and is not employed by the individuals conducting the study.

## CONSENT

By signing this consent form you are agreeing that the study has been explained to you and that you understand the study, and your questions have been answered.

**PARTICIPATION IN RESEARCH IS VOLUNTARY.** You may decline to participate or to withdraw at any point in this study without jeopardy to any present or future medical care you may require. You are signing that you agree to take part in the study. You will be given a copy of this consent form. By signing this form, you will not give up any of your legal rights.

I agree to participate in this study.

\_\_\_\_\_  
Subject's signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Physician

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness

\_\_\_\_\_  
Date

## APPENDIX IX: ACSR SPECIMEN PREPARATION & SHIPPING INSTRUCTIONS

### COLLECTION

Consent patient for ACSR donation. Collect **20 cc** of whole blood in acid citrate dextrose (ACD) tubes.

### SHIPPING

To ship, place the tubes into a canister of a STP-100 SAF-T-PAK shipper wrapping each tube in bubble wrap and using the absorbent paper at the bottom of the canister. Each sample tube should be labeled using a sharpie pen (permanent marker) with the following information:

- Protocol #: AMC 045
- AMC Patient ID#
- Date and time of collection
- Specimen type, i.e., WB=Whole Blood, P=Plasma, S=Serum
- Specimen purpose: Donation

Place the lid on the canister and place it inside of the ambient SAF-T-PAK shipper. Fold and pack ACSR form inside shipping box. Seal the ambient shipper with cellophane shipping tape. Label the ambient shipper with the "UN 3373" diamond shaped label. On one side, in black marker write, your name or name of responsible person, date of collection and phone number of the person responsible for the package.

**Specimen Shipment:** Specimens are accepted MONDAY through THURSDAY. Specimens are not accepted on Friday.

All **BLOOD (whole blood, plasma, serum)** specimens should be shipped by overnight express at room temperature to:

ACSR Blood Receiving Laboratory  
Johns Hopkins University  
1650 Orleans Street, CRB-384  
Baltimore, MD 21231-1000  
TEL: (410) 955-8721  
FAX: (443) 287-3217

All **TISSUE** specimens should be shipped by overnight express to:

Dr. Sylvia Silver  
George Washington University Medical Center  
2300 I Street, NW  
Room 507  
Washington, DC 20037  
Phone: (202) 994-1444  
Fax: (202) 994-5056



Please use the AMC Operations Center FedEx account [REDACTED]

### **Instructions for specimens collected on Friday:**

## **PREPARATION OF PLASMA AND MONONUCLEAR CELLS**

It is preferable that separation occurs as soon as possible. If necessary, whole blood in acid citrate dextrose (yellow top tube) can be held at room temperature for no more than 24 hours.

### Materials:

- Lymphocyte Separation Medium (LSM Solution, Ficoll-Hypaque - sterile)
  - 15 ml conical centrifuge tubes (sterile)
  - PBS (sterile)
  - 1, 5 ml and 10 ml serologic pipettes (sterile)
  - NUNC tubes
  - Alcohol-saturated, control rate freezer container
  - DMSO freezing media:
    - 50% Cryoprotective Medium, Cambrex (catalog no.:12-132A)
    - 50% Heat Inactivated Fetal Bovine Serum
1. Preparation of Plasma Samples
    - a. The 7 ml tube of whole blood in acid citrate dextrose should be rotated gently 2 or 3 times before being centrifuged. Do not transfer before centrifugation.
    - b. The cells are separated by centrifugation at 500 g for 10 minutes.
    - c. 0.5 ml aliquots of plasma are removed and put into 1.5 ml screw top tubes and transferred to liquid nitrogen storage.
  2. Peripheral Blood Mononuclear Cell Separation and Freezing
    - a. The cells and plasma remaining from the previous step are transferred into a 15 ml conical tube, capped and re-suspended by gently tapping the bottom of the tube.
    - b. Sterile PBS should be added to the suspended cells until the final volume is 8 ml; invert to mix.
    - c. The 8 ml whole blood-PBS mixture should be carefully overlaid onto 4 ml of room temperature LSM or Ficoll-Hypaque solution in a sterile 15 ml conical tube. A sharp interface should exist between the LSM and the whole blood mixture. (If the layer of LSM gets mixed with the blood-PBS, the tube should be gently rotated to mix the blood, PBS, and LSM, and transfer to a 50 ml sterile conical tube. An equal volume of PBS is added, and the cells are separated at 600 g for 15 minutes. After removal of LSM-PBS supernatant, return to Step b).
    - d. The 15 ml conical tube for 30 minutes at 900 g at room temperature. The mononuclear leukocytes (principally lymphocytes and monocytes) will band at plasma/LSM interface.
    - e. The fluffy white layer just below the plasma layer should be aspirated off, along with approximately half of the LSM layer under it, and transferred to an appropriately labeled 15 ml sterile conical centrifuge tube. Mix by gentle rotation.
    - f. Washed twice in sterile PBS - centrifuge at 500 g for 10 minutes.

- g. Cell pellet should be mixed well with a gentle finger-tapping action.
- h. Using a 1 ml pipette, the \*DMSO freezing mixture should be added drop wise to the cell pellet suspension. Gently finger-tap between drops. If the cell pellet is small, only 0.5 ml of freezing media is added (and only one aliquot of cells is frozen). If the cell pellet is large, up to 2 ml of freezing media can be added in a drop wise fashion. (Cell densities of 1 - 10 million PBMC/ml are best for cryopreservation. If a hemocytometer is available, the optimal concentration is 5 million PBMC/ml).

**\*Important-Do not put the DMSO containing media on the cell button all at once.**

- 3. Freeze the cell suspension in 0.5 ml aliquots in sterile NUNC vials by placing the NUNC tubes in a room temperature, alcohol saturated, control rate freezer container and store in the -80°C freezer overnight. Transfer the cell suspension into the liquid nitrogen temperature freezer for long-term storage the next working day.

\*\*\*PLEASE DOUBLE CHECK PACKAGING OF SHIPPER AND DO NOT DEVIATE FROM REQUESTED LABELING. Shipping frozen aliquots requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.

**Please Note:** The shipper will be mailed back to the AMC site.

The STP-210 SAF-T-PAK shipper is a complete kit w/ all trappings, bubble wrap, absorbent paper, labels, everything (but to reuse the shipper, you will need new labels, wrap, etc).

## RECORD OF SPECIMENS

This study will track specimens via GlobalTrace<sup>SM</sup>, a component of the AMC AdvantageEDC<sup>SM</sup> system. The GlobalTrace<sup>SM</sup> shipment manifest must accompany all specimen shipments.

## APPENDIX X: AMC DATA SAFETY MONITORING PLAN (Version 5.0 · January 28, 2014)

### **Monitoring the Progress of Trials and the Safety of Participants**

All AMC protocols that collect safety data follow the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (<http://ctep.cancer.gov/guidelines/index.html>). All adverse events that meet the NCI's expedited reporting requirements are reported to the Investigational Drug Branch (IDB) of the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application. All expedited adverse event reports are also required to be submitted to the local Institutional Review Board (IRB) of the reporting institution. If NCI holds the IND or no IND is required for a study, the AMC site reports serious adverse events directly to the AMC Operations and Data Management Center (ODMC) via CTEP-AERS. In some instances, the AMC sites may report serious adverse events directly to a commercial sponsor holding the IND, who will then report the event to the AMC ODMC. Most AMC protocols require sites to report all serious adverse events via CTEP-AERS and the AMC ODMC to forward a copy of the report to the sponsor. The AMC ODMC also distributes all IND safety reports to all investigators upon receipt, and makes these reports available on the password-protected section of the AMC Operations web site. Unless an AMC protocol specifies an alternate plan for the review and submission of serious adverse events, all serious adverse events received by the AMC ODMC will be reviewed by the AMC Medical Monitor at the AMC ODMC prior to submission to NCI and the sponsor. For protocols for which the IDB does not have an assigned drug monitor to review serious adverse event reports, in the event of disagreement between the reporting physician and the AMC Medical Monitor regarding the attribution of the event to the investigational agent(s) (i.e., determination of whether the relationship is unrelated, unlikely, possible, probable, or definite), the AMC Medical Monitor will provide the final determination of the relationship.

The AMC ODMC provides listings of all reported adverse events and serious adverse events to the Protocol Chair and Co-chair(s) for review on a regular basis. The AMC ODMC compiles these events in a tabular format and posts them on the password-protected section of the AMC web site where these reports are updated nightly. The AMC web site is accessible to all AMC investigators, co-investigators, and their staff. Email notification that this information is available on the web site will be sent to all site PIs. It is the responsibility of each site to provide this information to their respective IRBs, if required by their IRB. For blinded studies, the serious adverse events are reviewed and tabulated without treatment assignment. The AMC Medical Monitor will review listings of all reported adverse events on a quarterly basis for safety concerns.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the Protocol Chair and also by the appropriate disease-oriented Working Group during scheduled conference calls. For phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the Protocol Chair, AMC Medical Monitor, and Group Statistician determine whether these criteria have been met. For phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage phase II

trial, is based on meeting criteria stated in the protocol, and the Protocol Chair, AMC Medical Monitor, and Group Statistician determine whether these criteria have been met.

For phase III trials, the AMC has formed an independent Data Safety and Monitoring Board (DSMB). Voting members of the DSMB are physicians, a statistician, and a patient advocate. All voting members are from outside the AMC. Nonvoting members are the AMC Group Statistician, the Statistician listed on the protocol, an AMC Operations Center staff member, two representatives (normally a clinician or statistician) from the Office of HIV AIDS Malignancy (OHAM) or from the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, of the National Cancer Institute (NCI). The AMC Data Safety and Monitoring Board reviews AMC phase III studies in accordance with the National Cancer Institute's Policy for Data Safety and Monitoring. Confidential reports of all phase III trials are prepared by the AMC Group Statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the AMC DSMB Charter. This report addresses specific toxicity concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB Chair to the Group Chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The Group Chair is then responsible for notifying the Protocol Chair and relevant Disease-oriented Working Group Chair before the recommendations of the DSMB are carried out. In the unlikely event that the Protocol Chair does not concur with the DSMB, then the NCI Division Director or designee must be informed of the reason for the disagreement. The Study Chair, relevant Disease-oriented Working Group Chair, Group Chair, DSMB Chair, and NCI Division Director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a formal amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, a summary of the serious adverse events reported to the DSMB is posted to the AMC web site. It is each site's responsibility for conveying this information to its IRB.

### **Plans for Assuring Compliance with Requirements Regarding the Reporting of Adverse Events (AE)**

For trials monitored by the NCI's Clinical Data Update System (CDUS), adverse event information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), adverse event information is transmitted electronically to NCI every two weeks.

The Protocol Chair, AMC Group Chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with the protocol requirements for adverse event

reporting. All AMC investigators certify compliance with NCI and FDA requirements for adverse event reporting by signing the AMC Adherence Statement for site membership, the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration and IND studies sponsored by AMC investigators. Investigators are responsible for identifying and reporting all adverse events to the AMC ODMC, CTEP-AERS, and/or sponsors according to the protocol requirements, and assuring compliance with reporting to the local IRB. Protocol compliance with adverse event reporting requirements is assessed by the AMC ODMC during routine site monitoring visits by reviewing the site's source documentation.

The data entry system used for AMC studies, AdvantageEDC<sup>SM</sup> (a web-based data entry and enrollment system), is programmed to notify the site investigator, protocol chair, and AMC ODMC via email in the event that a site reports an adverse event that meets expedited reporting criteria to NCI and/or FDA. If the site does not follow with a CTEP-AERS report, the AMC ODMC contacts sites to request an expedited report. Additionally, the protocol chair, AMC ODMC, and the AMC Medical Monitor review reported adverse events on a routine basis to identify adverse events reported by sites that require expedited reporting via CTEP-AERS. The Protocol Chair, AMC Group Chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

#### **Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant**

In the event that termination of the trial or major modification to the protocol is under consideration, the Protocol Chair will convene the AMC Data Coordinator and Disease-oriented Working Group Chair by conference call to discuss the options. For phase I and II trials, the Protocol Chair also has the option of asking the AMC DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO) when studies are temporarily or permanently closed. The Cancer Treatment and Evaluation Program (CTEP) of the National Cancer Institute (NCI) must approve all protocol amendments prior to distributing to the AMC sites.

#### **Plans for Assuring Data Accuracy and Protocol Compliance**

All study data for AMC clinical trials are entered directly by AMC site staff into AdvantageEDC<sup>SM</sup>. During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. AMC ODMC staff routinely interacts with site staff to resolve any data problems.

In accordance with NCI guidelines, the AMC ODMC conducts monitoring visits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site Principal Investigator and to the

NCI. In the event that major violations are identified, sites are asked to provide a plan to correct deficiencies within 30 days. If needed, a repeat site visit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option of taking action against the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site investigators or staff members.